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Synthesis of 3-carbomethoxy-2,5-dihydrothiophenes ; Diels- Alder reactions of 2-carbomethoxy-1,3-butadiene.

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**LA THÈSE A ÉTÉ
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SYNTHESIS OF 3- CARBOMETHOXY-2,5- DIHYDROTHIOPHENES;
DIELS- ALDER REACTIONS OF 2- CARBOMETHOXY-1,3- BUTADIENE

BY

ROBERT A. SIELER

A THESIS

Submitted to the Faculty of Graduate Studies through the
Department of Chemistry in Partial Fulfillment
of the Requirements for the Degree
of Master of Science at the
University of Windsor

Windsor, Ontario

1979

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710359

To My Parents

ABSTRACT

3- Carbomethoxy-2,5- dihydrothiophenes are easily prepared by the reaction of α - mercaptocarbonyl compounds with substituted α - phosphonylacrylates. These latter compounds are prepared from methyl diethylphosphonoacetate in excellent yields.

The dihydrothiophenes are oxidized to sulfones with m- chloroperbenzoic acid and form dienes by thermal sulfur dioxide elimination. A survey of the Diels- Alder reactions of 2- carbomethoxy-1,3- butadiene with representative dienophiles showed that only electron- deficient dienophiles react well and mixtures of regio- isomers are frequently formed.

ACKNOWLEDGEMENTS

I am grateful to Dr. G.W. Wood, ably assisted by my research advisor, Dr. J.M. McIntosh, for without their dedicated efforts this thesis would not have been written at this time.

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CHAPTER 1

INTRODUCTION

The modern organic chemist is remarkably similar to his alchemist forefather. While the alchemist was concerned with the reaction of turning base- metals into gold, the organic chemist deals with the interactions of atoms and/or molecules to form new compounds, hopefully beneficial to society.

However complex the target molecule, its stereo- and regiospecific synthesis depends, more often than not, on the availability of a number of smaller molecules which possess known stereochemistry. The synthesis of these "building blocks" is a field of organic chemistry in itself.

The Diels- Alder reaction consists of the addition of a compound containing a double or triple bond (the dienophile) to the 1,4- positions of a conjugated diene system (the diene), with the subsequent formation of a six-membered hydroaromatic ring. The configuration of the product conforms to general principles (1) commonly known as the Alder rules.

Since its discovery by Otto Diels and Kurt Alder (2) in 1928, who subsequently received the 1950 Nobel Prize in chemistry for their work, the Diels- Alder reaction (3) has been of inestimable aid in the stereospecific synthesis of a

number of natural products such as reserpine (4), cortisone (5) and yohimbine (6). Dienophiles may be obtained in a number of ways; the more common ones are commercially available. The major difficulty arises in the preparation of the required diene.

Methods of diene preparation are varied, among them being the acid hydrolysis of allylic alcohols (7), the dehydration of allylic alcohols with KHSO_4 and POCl_3 , (both of which may isomerize, dimerize or polymerize the diene (8)), the base-catalyzed dehydrohalogenation of allylic halides (9) and the Wittig reaction (10). Dienes may also be synthesized by the treatment of a saturated phosphonyl-stabilized anion with an unsaturated aldehyde or ketone, producing 4-alkyl-2,4-pentadienoates in 50-65% yield (11) (Figure 1).

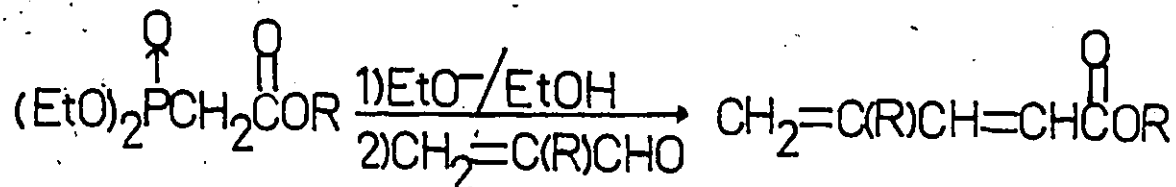


Figure 1. Phosphonates in Diene Preparation.

Transition metal complexes have been used in conjugated diene synthesis. Examples are the coupling of vinyl halides to olefins (12) (Figure 2) and the conversion of allylic

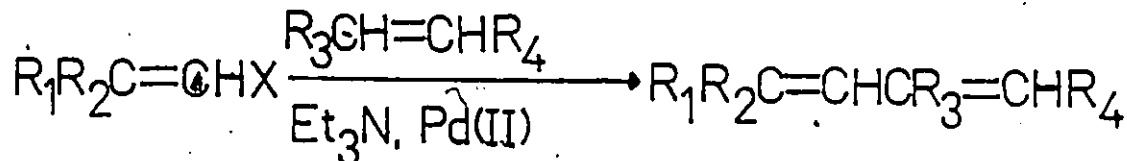


Figure 2. Palladium Catalyzed Linking of Olefins.

ethers to dienes (13). (Figure 3). Vinyl Grignard reagents may

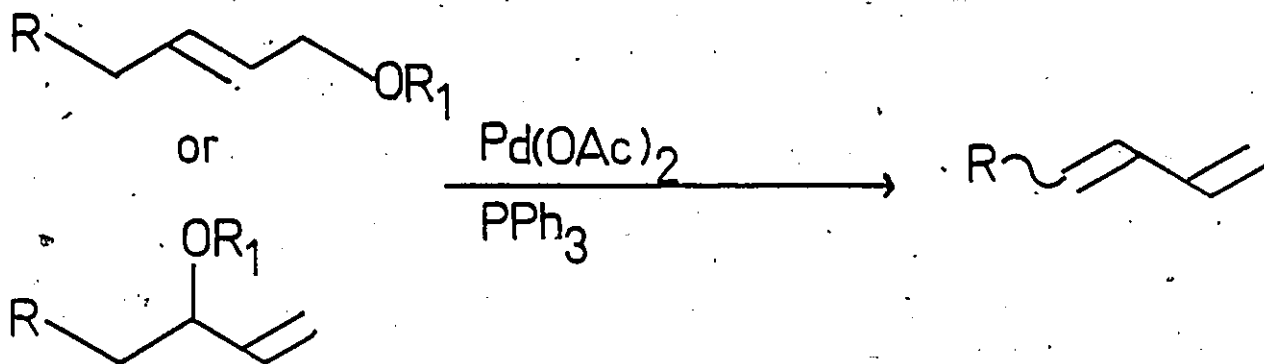


Figure 3. Palladium Catalyzed Conversion of Allylic Ethers To Conjugated Dienes.

also be coupled to form 1,3- dienes (7, 14). Recently, α, β - unsaturated ketones have seen service in the preparation of 1,3- diphenyl-4- alkyl-1,3- dienes (15), in yields varying from 65-86% (Figure 4).

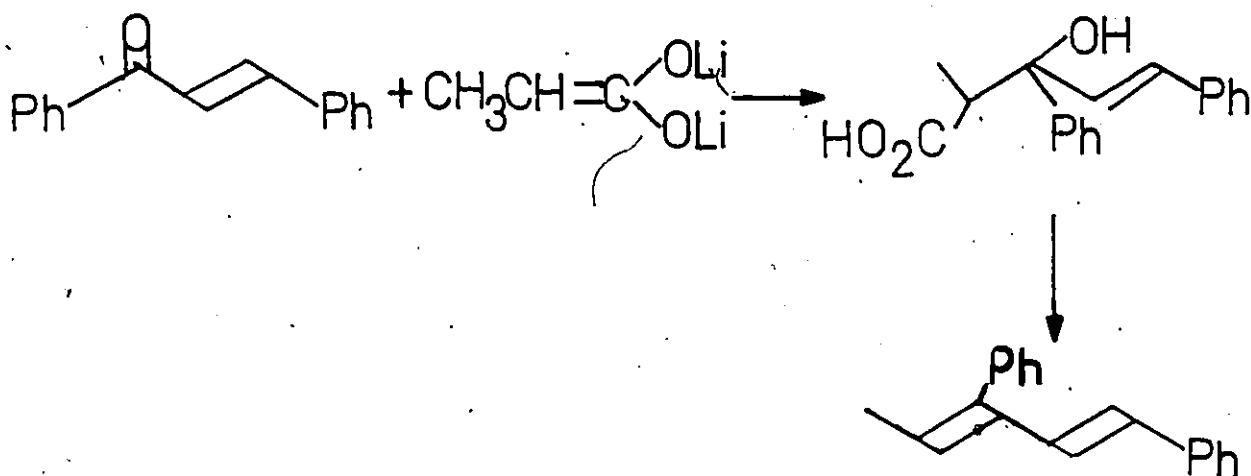


Figure 4. Preparation of Dienes via Organo- Lithium Reagents.

While many of the afore- mentioned reactions are regio- specific, the stereochemistry of the newly formed diene is difficult to predict, there is a lack of stability of functional groups to reaction conditions and yields are sometimes low.

Industrially, the thermal decomposition of 2,5-dihydrothiophene sulfones 2 is used as the final step in the purification of diene mixtures. It has been found that the thermal decomposition of these sulfones proceeds in a regiospecific and stereospecific disrotatory manner at relatively low temperatures (16, 17, 18). (Figure 5).

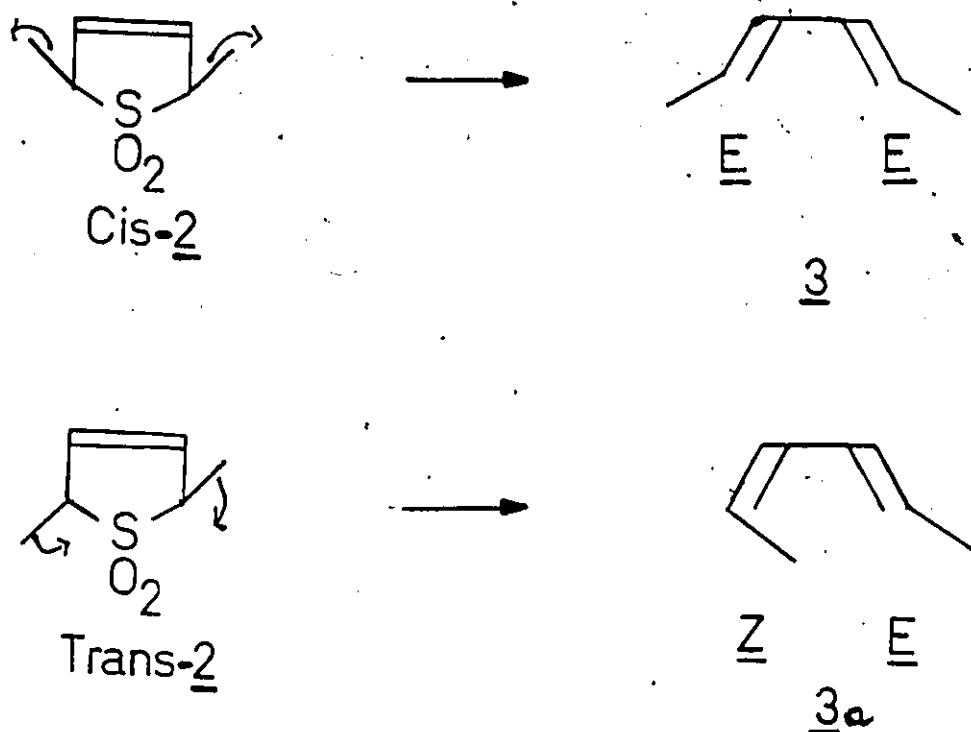


Figure 5. Sulfone Pyrolysis.

Compounds of type 2 are most easily prepared by the cheletropic addition of sulfur dioxide to a conjugated diene or the oxidation of the corresponding 2,5-dihydrothiophene (19). Clearly, the former method is unsuitable as a diene synthesis since these are required as starting materials.

Methods for the preparation of 2,5-dihydrothiophenes include the Michael-type cyclization of a mercaptomuconate (20),

the partial reduction of thiophenes with alkali metals in liquid ammonia (21, 22), and the conjugate addition-cyclization reaction between α -mercaptoesters and α,β -unsaturated esters (23). These reactions suffer from low yields and the substitution patterns on the dihydrothiophene ring are limited.

Because of the limited accessibility of 2,5-dihydrothiophenes, McIntosh (24, 25, 26) and co-workers launched an extensive study directed toward the general synthesis of 2,5-dihydrothiophenes (Figure 6). These were synthesized

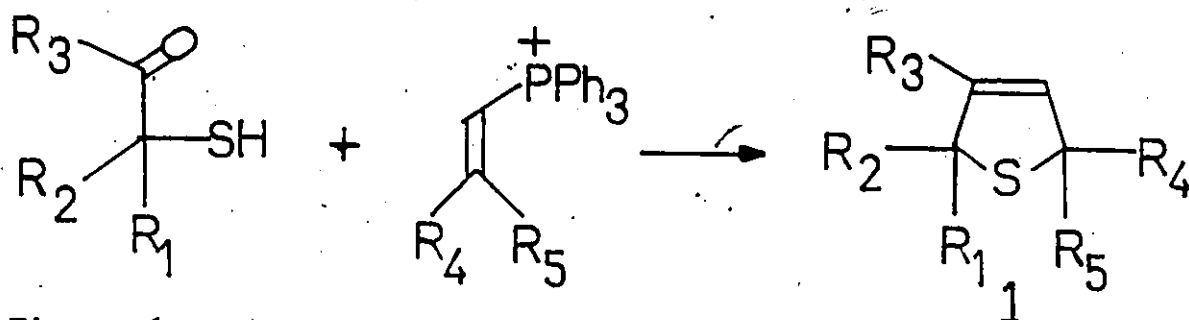


Figure 6. Synthesis of 2,5- Dihydrothiophenes.

by a combined Michael- Wittig reaction sequence using α - mercaptocarbonyl compounds and substituted vinylphosphonium salts. The mechanism of the reaction is outlined in Figure 7.

Peracid oxidation of the intermediary 2,5- dihydrothiophenes **1** furnished sulfones **2** , whose thermal decomposition gave dienes **3** , the stereochemical composition of which defined the cis/trans ratio of the synthesized dihydrothiophenes (27). The synthesis, employing pyridine as solvent and triethylamine as base was quite successful for alkylated compounds.

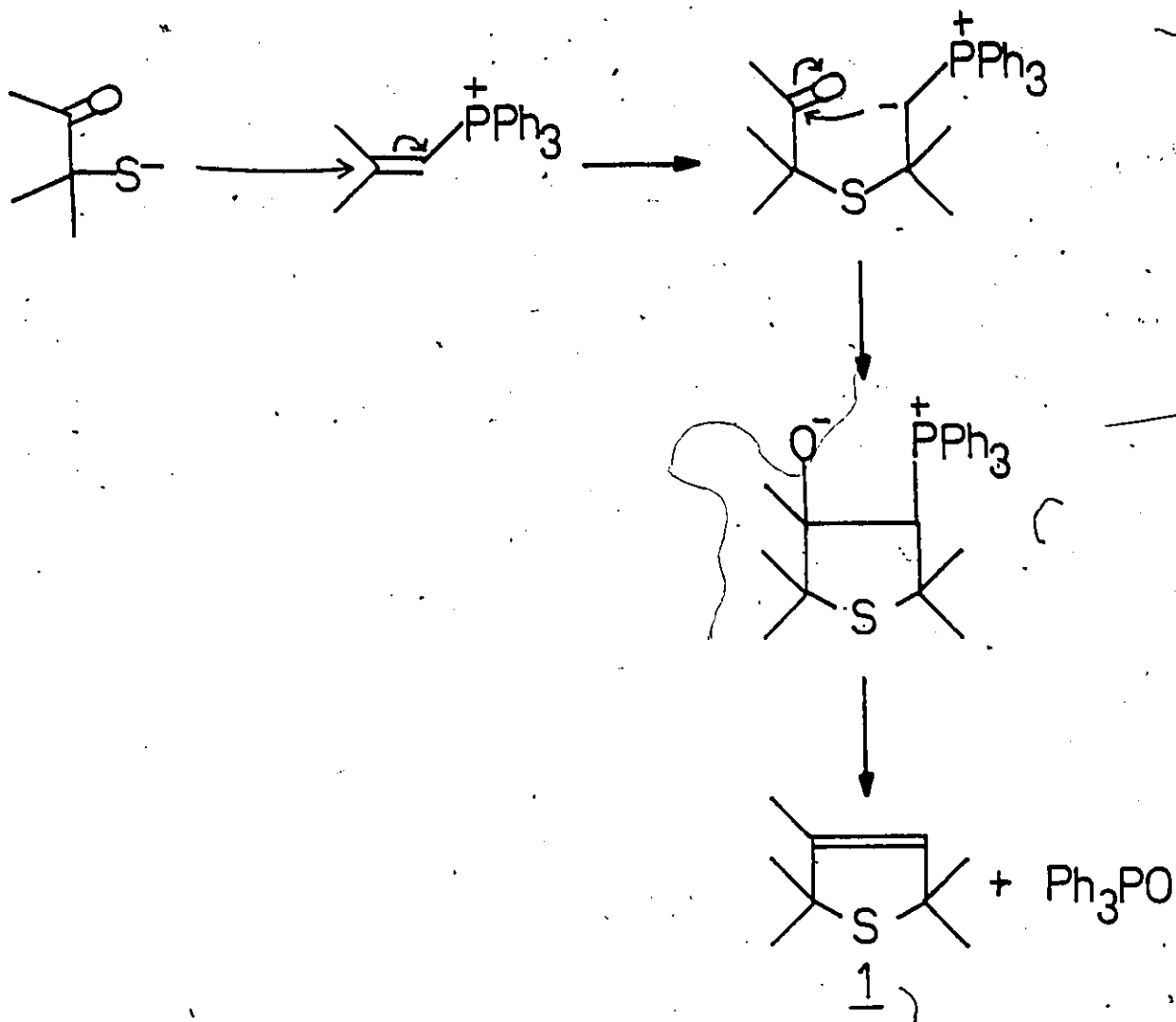


Figure 7. Mechanism of Dihydrothiophene Formation Employing
 α - Mercaptocarbonyl Compounds and Vinylphosphonium
Salts.

The importance of alkylated dihydrothiophenes has been demonstrated in several instances. McIntosh and Khalil (28) have shown that dihydrothiophenes may be easily oxidized to the corresponding thiophene employing chloranil as the oxidizing agent. Thiophenes have been used as dienes in the Diels- Alder reaction (Figure 8).

Reductive desulfurization of 2,5- dihydrothiophenes

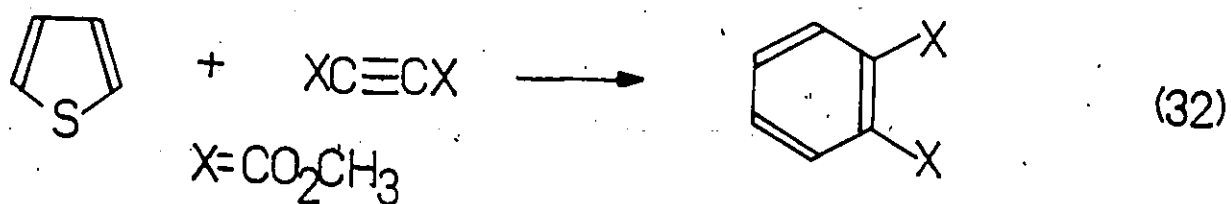
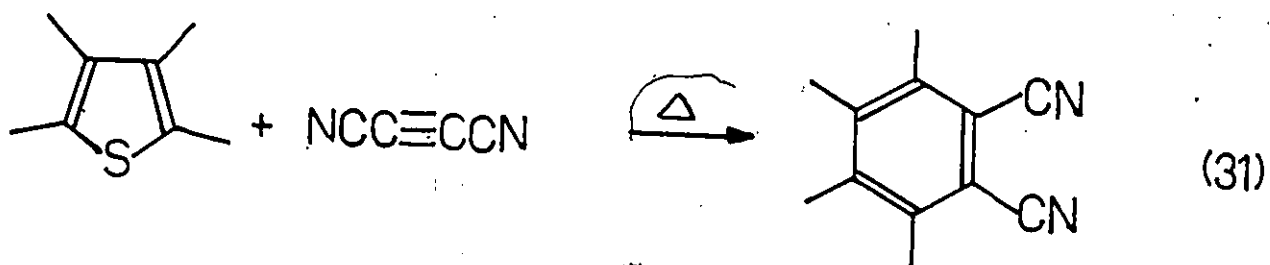
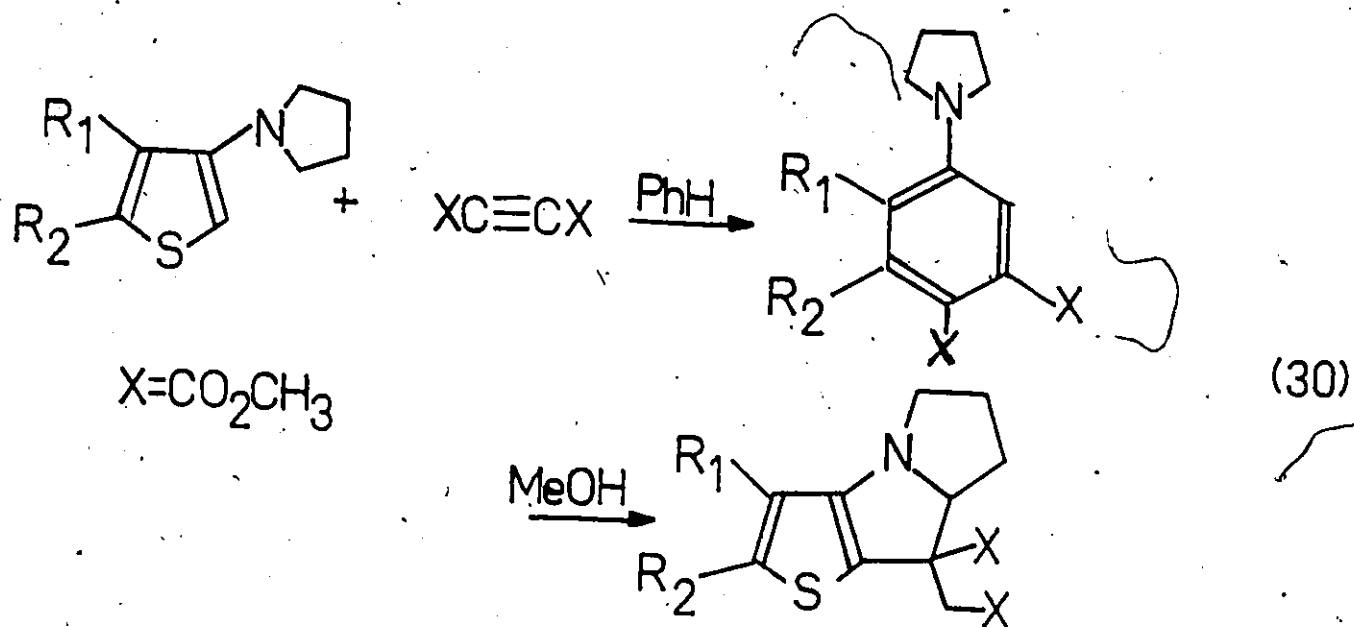
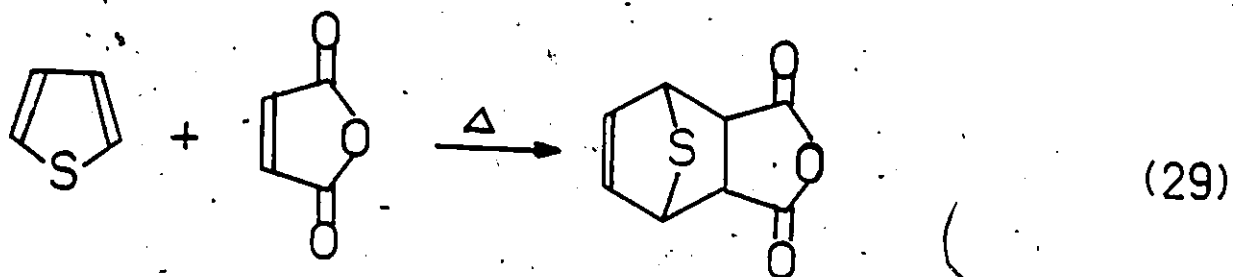
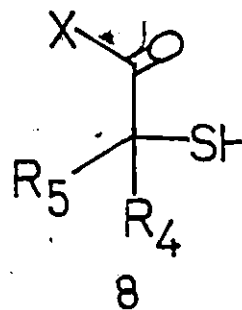
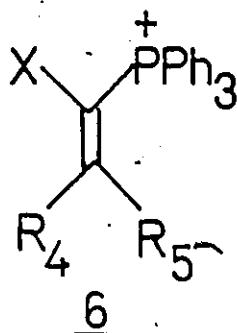
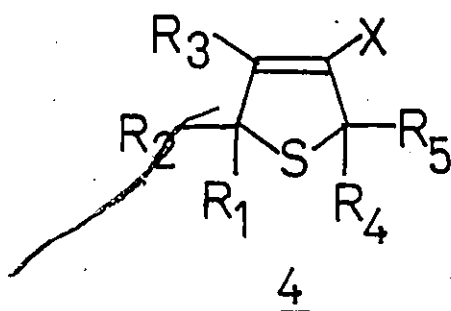


Figure 8. Thiophenes Used as Dienes.

would afford a facile synthesis of stereo- and regiospecific cis-olefins. Many reagents have been employed in reductive desulfurization, such as Raney Nickel (33) and lithium in ethylamine (34). Tributyltin hydride has been shown to produce dienes when reacted with 2,5-dihydrothiophenes (35).

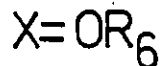
While the procedure developed by McIntosh (24, 25, 26) was successful for the synthesis of alkylated compounds, functional groups attached to the 3-position of the dihydrothiophene ring presented difficulties. For example, methoxy or carboalkoxy-substituted dienes would require the synthesis of dihydrothiophenes of general structure 4 or 5.



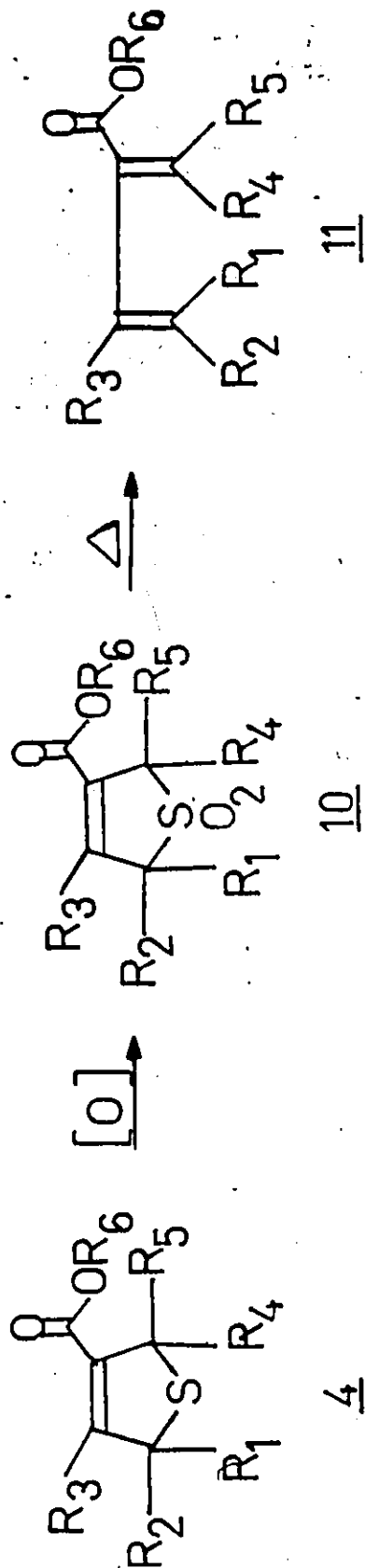
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9



The importance of functionalized dihydrothiophenes of type 4 lies in their ready conversion to functionalized dienes. While terminally carboxylated conjugated dienes can be prepared using Knoevenagel-type conditions (36), or the condensation between carboxylated phosphonates and α,β -unsaturated aldehydes and ketones (11), compounds of type 11 (Figure 9) cannot, and their use in the Diels-



R_{1-5} = Alkyl or Hydrogen

R_6 = Alkyl

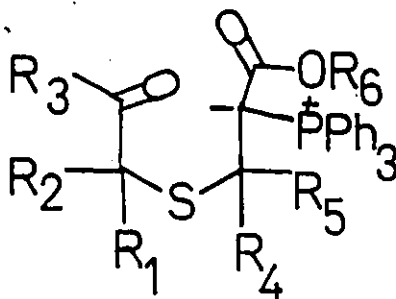
R_{1-5} = Hydrogen

R_6 = Methyl

Figure 9. Proposed 2- Carboxylated-1,3- Conjugated Diene
Synthesis.

Alder reaction makes them of considerable synthetic interest. The parent compound 14 (37) rapidly polymerizes, and the possibility of storing 14 in the form of sulfone 13, which may easily converted to 14 as required was an attractive possibility. In addition, Stork and Stotter (38) have shown that 4 has excellent dienophilic character and desulfurization of the Diels- Alder adducts may lead to the production of complex organic compounds.

Where the previously mentioned reaction sequence used, it would necessitate the use of 8 or 9 as the mercapto-carbonyl compound or 6 or 7 as the vinylphosphonium salt. A single example of 7 is known (39), but it does not react satisfactorily in the annulation reaction (26). Attack of the thiolate ion on 6 would result in the formation of a phosphorane of type 15, which is known to react with aldehydes (40), but very poorly (41), or not at all (42) with ketones.



15

α -keto- β -mercaptoesters 8 offer two difficulties; they are difficult to prepare and offer two sites for attack by the phosphorane, resulting in the possible formation of three products (Figure 10). Esters 9 do not generally give

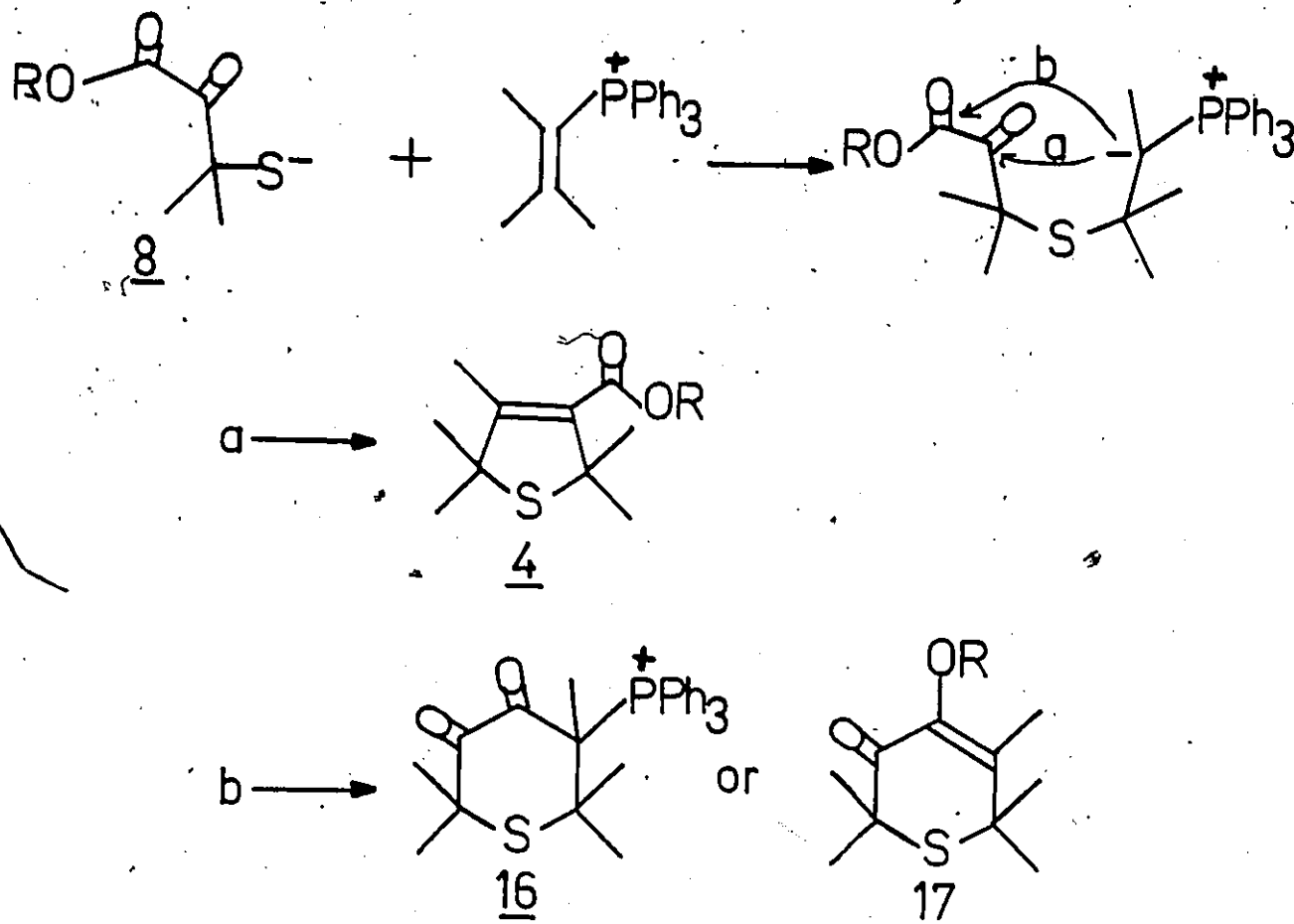


Figure 10. Products Possible From The Reaction of 8 With Vinylphosphonium Salts.

olefins on treatment with a phosphorane (43), although some exceptions are known (44).

It is known that a carbanion located adjacent to a phosphorus atom carrying a high degree of positive charge is stabilized by overlap of the orbital carrying the lone pair of electrons with a vacant 3d- orbital of the phosphorus atom. The best examples of such systems are the phosphonium ylids. The α - anion of a phosphonate can be considered as a resonance hybrid having three contributing structures (Figure 11). Structures 18 and 20 make use of an empty 3d- orbital on the phosphorus in a manner similar to the

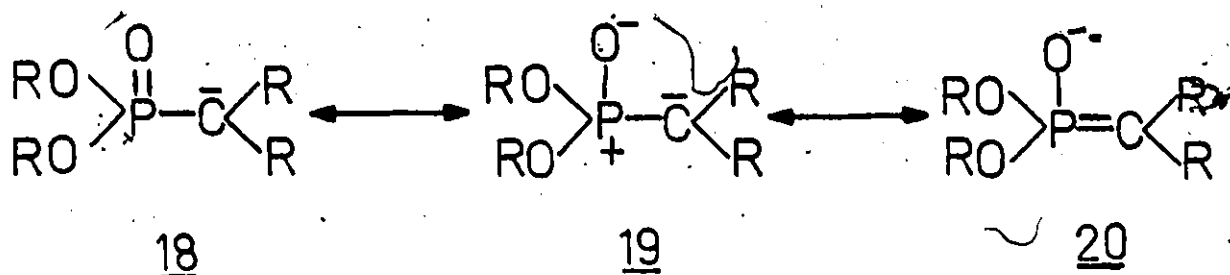
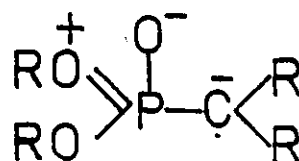


Figure 11. Resonance Structures of a Phosphonate Anion.

phosphoranes. Such dp- π bonding is appreciable in the case of phosphoranes and leads to appreciable stability of the carbanion (10). Phosphonate carbanions will be stabilized to a lesser extent due to back donation from oxygen (21), and, as a result, should be more nucleophilic than the phosphoranes.



21

The most extensive study of the utility of phosphonate carbanions in the synthesis of olefins was conducted by Wadsworth and Emmons (45), who found that phosphonate carbanions containing electron-withdrawing groups reacted with aldehydes or ketones under fairly mild conditions to produce olefins. The analogous reaction using triphenylphenacylidene phosphorane with benzaldehyde required thirty hours refluxing in tetrahydrofuran (46).

Based on the preceding facts, the use of vinylphosphonates was an attractive possibility.

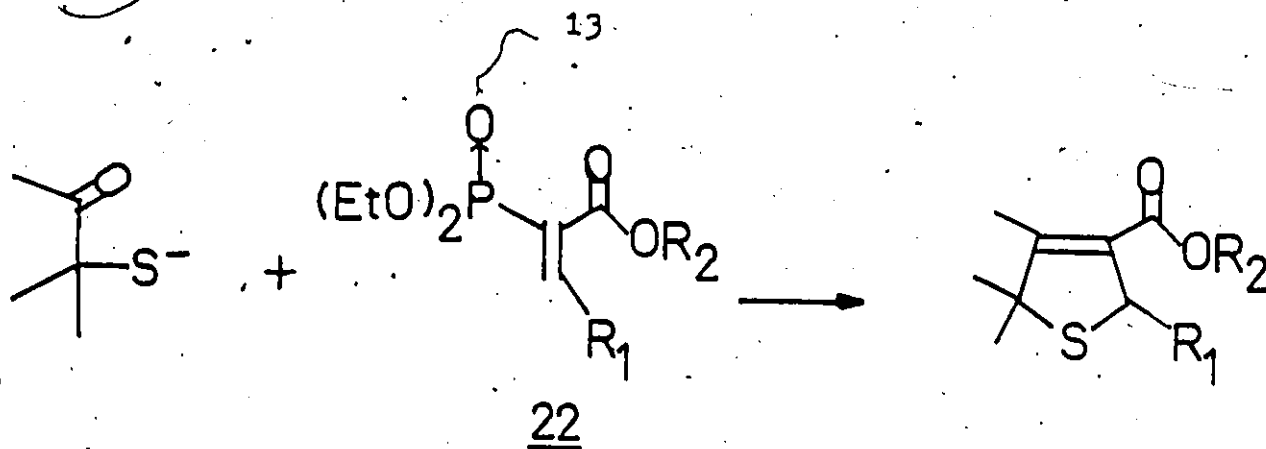


Figure 12. Synthesis of 3- Carboxylated 2,5- Dihydrothio-
phenes Using Vinylphosphonates.

Furthermore, vinylphosphonates of type 22 have been known to undergo addition reactions with nucleophiles (47, 48, 49), and there is evidence in the literature that a Wittig- type reaction of phosphonate carbanions, commonly called the Horner- Emmons modification of the Wittig reaction only proceeds well when electron- withdrawing substituents are adjacent to phosphorus (50). This fact makes 22 well suited for a proposed 3- carboalkoxy-2,5- dihydrothiophene synthesis. The mechanism of the reaction of phosphonates with carbonyl compounds is analogous to that for the Wittig reaction, and it was anticipated that the mechanism for dihydrothiophene formation would be identical to that when phosphonium salts were used (Figure 13).

Further advantages of vinylphosphonates, aside from their increased nucleophilicity over the corresponding phosphoranes are:

1. Separation of the products from water soluble diethyl phosphate is much easier than separation from triphenylphosphine oxide.

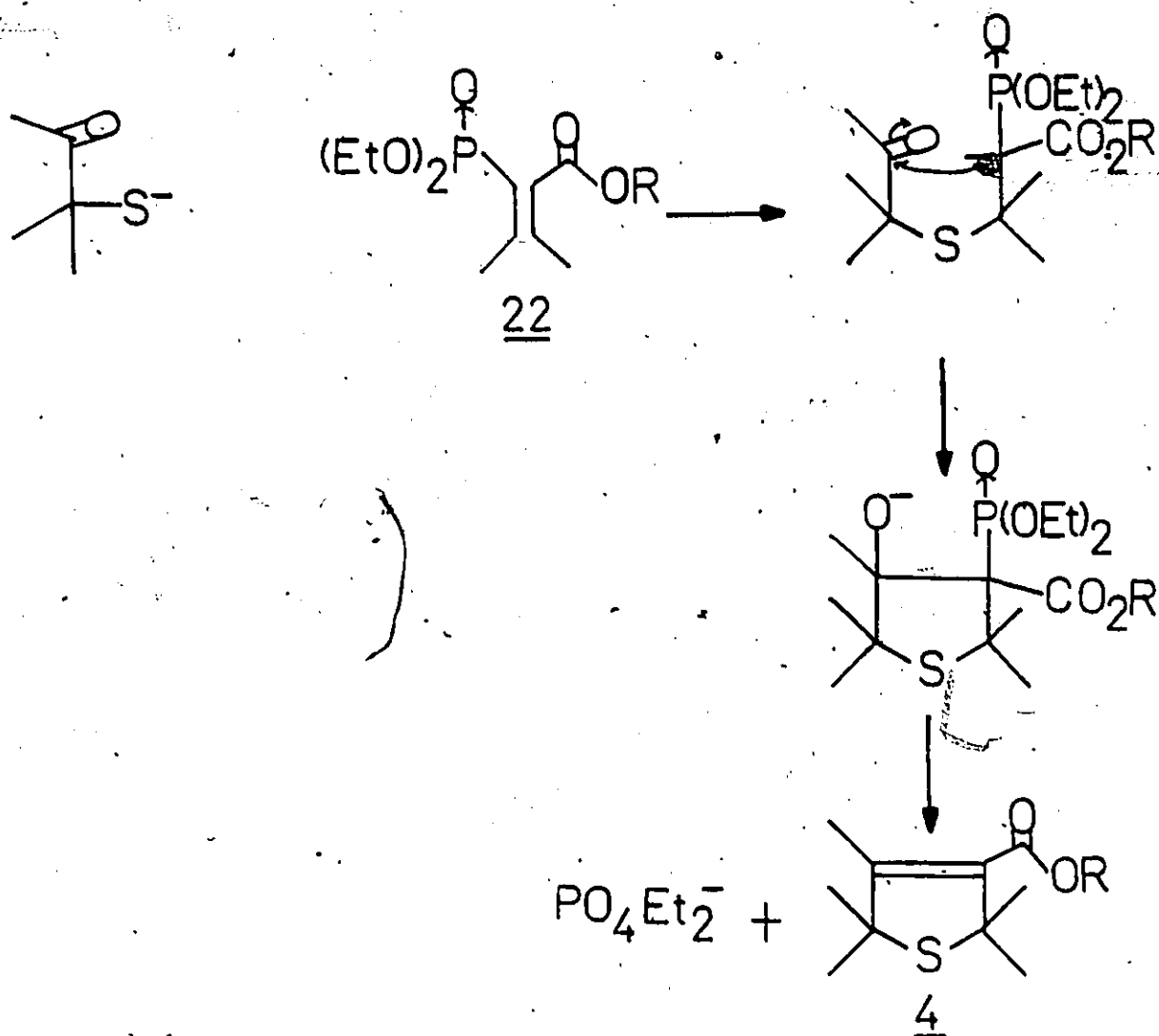


Figure 13. Mechanism of 3- Carboalkoxy-2,5- Dihydrothiophene Formation.

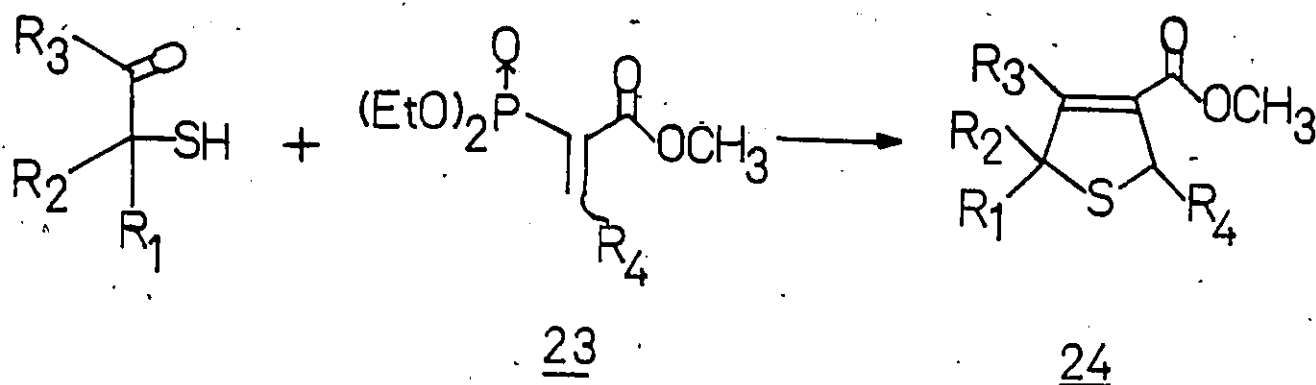
2. Phosphonates are readily prepared using the Michaelis-Arbuzov reaction (51) and are cheaper than phosphonium salts.

With these facts in mind we set out to explore the preparation of vinylphosphonates 22 and their use in the synthesis of substituted 3- carboalkoxy-2,5- dihydrothiophenes.

CHAPTER 2

RESULTS AND DISCUSSION

In order to make use of the Michael- Horner- Emmons reaction sequence between α - mercaptocarbonyl compounds and vinylphosphonates for the synthesis of 3- carbomethoxy-2,5-dihydrothiophenes, it was necessary to establish efficient means of synthesizing starting materials.



R₁₋₄ Alkyl, Ph or Hydrogen

Figure 14. Synthesis of 3- Carbomethoxy-2,5-Dihydrothiophenes

The preparation of α - mercaptoketones and α - mercaptoaldehydes are established procedures (25,27). In contrast to vinylphosphonium salts, which, in recent years have found great applicability in organic synthesis (10), vinylphosphonates have not been so extensively studied. While there are a

considerable number of vinylphosphonates with varying functionality (52), reports on the preparation of 23 are not common. A number of pathways were available. Among them, the isomerization of allylic isomer 25, (Figure 15), was not pursued as previous studies had shown the difficulty of such an isomerization (53), and the preparation of 25 is a challenging synthetic problem in itself. Another approach

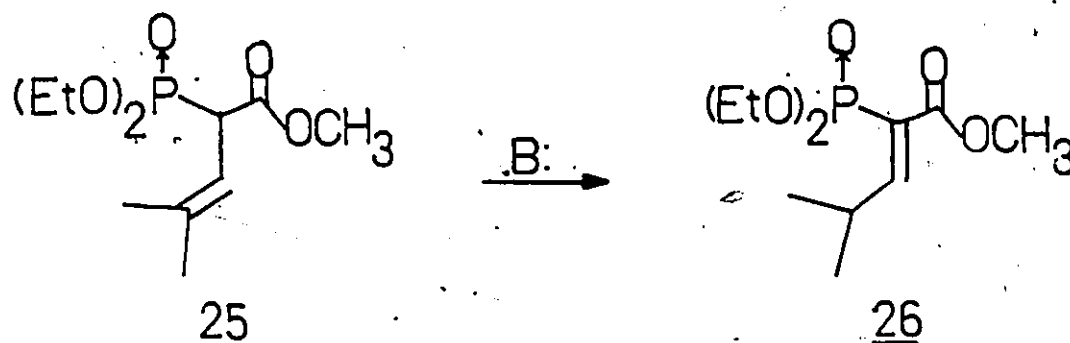


Figure 15. Isomerization of Allylic Phosphonates.

which was considered involved the use of tetraethyl methylene-bisphosphonate (27) (Figure 16). Treatment of 27 with sodium hydride, then methyl bromoformate would furnish methyl tetraethylbisphosphonoacetate (28). The subsequent Horner-Emmons reaction of 28 with an aldehyde would furnish vinylphosphonate 23. This procedure was abandoned in lieu of a variation of the method reported by Pudovik (54), who stated that a Knoevenagel-type condensation takes place between benzaldehyde and ethyl diethylphosphonoacetate (29), to yield ethyl 2-diethylphosphono-3-phenylacrylate (30) (Figure 17). An extension of Pudovik's work, by Patai and Schwartz (55), showed that 29 would undergo an aldol-type

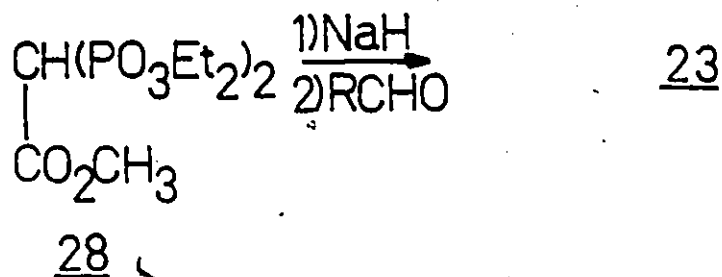
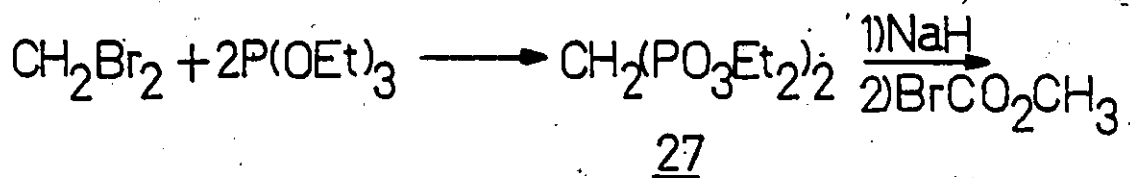


Figure 16. Synthesis of Vinylphosphonates Using Tetraethyl Methylenebisphosphonate.

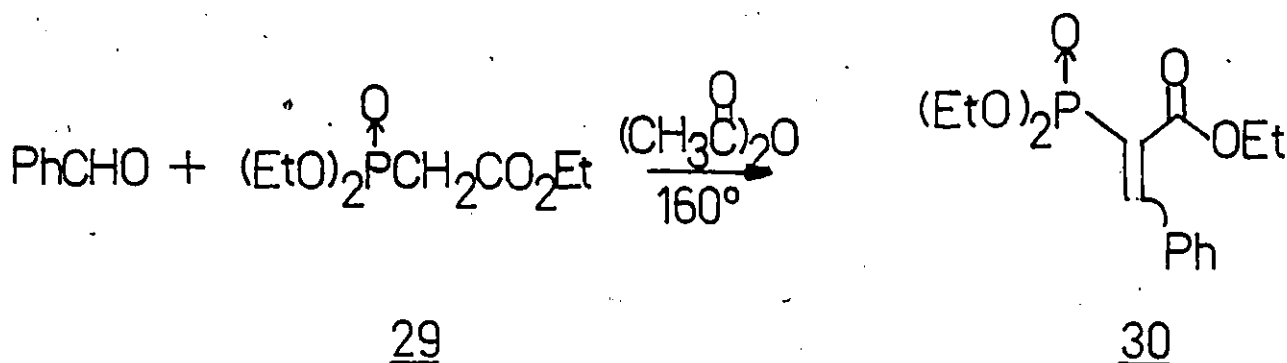


Figure 17. Knoevenagel- type Condensation Between Benzaldehyde and Ethyl Diethylphosphonoacetate.

condensation with benzaldehyde when refluxed in benzene solution containing catalytic amounts of piperidine and glacial acetic acid. Employing the procedure of Patai and Schwartz (55), from methyl diethylphosphonoacetate (31),

were obtained vinylphosphonates 32-34 (Figure 18). The

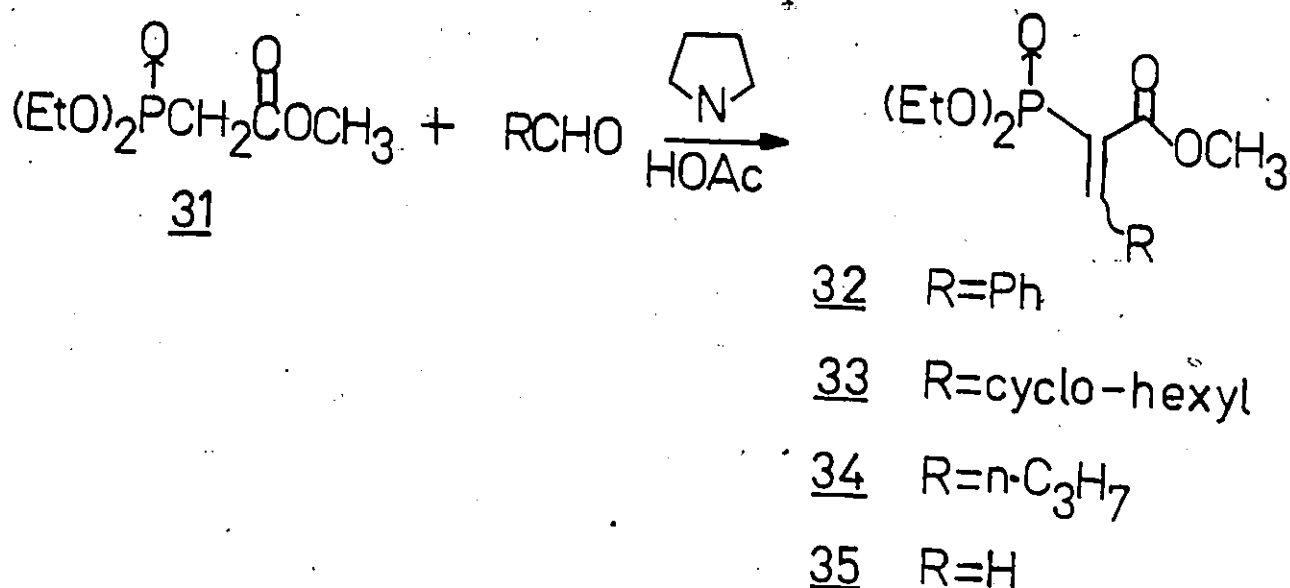


Figure 18. Vinylphosphonates Synthesized.

spectral data and physical constants are given in Tables 1 and 2.

When paraformaldehyde was used, 35 was obtained in only 16% yield, which was undoubtedly due to the very poor solubility of paraformaldehyde in benzene. Pudovik (56) reported that 35 could be prepared by refluxing 31 in methanol containing a catalytic amount of piperidine and one equivalent of paraformaldehyde. The extended workup procedure and distillation from a small amount of phosphoric acid provided 35 in low yields. A variation of Pudovik's procedure (56) was attempted and proved to be successful. Phosphonate 31 was refluxed in methanol containing one equivalent of paraformaldehyde and a catalytic amount of piperidine. Evaporation of the methanol afforded an oil, the nmr of which showed no vinyl absorption. This oil was

TABLE I
Vinylphosphonates

<u>Number</u>	<u>R</u>	<u>bp(°C/ Torr)</u>	<u>Yield(%)</u>
<u>32</u>	Ph	160- 165/1	70
<u>33</u>	cyclohexyl	120-122/0.02	97
<u>34</u>	n-propyl	96-102/0.05	87
<u>35</u>	H	92-94/0.08 ^a	76

a) Lit(49) 95-98/0.15

Lit(56) 100-101/1

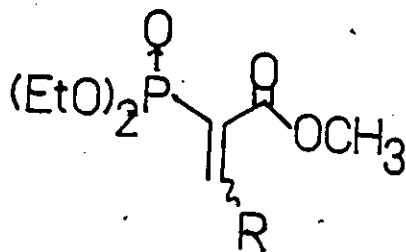


TABLE 2

Spectral Data For Vinylphosphonates

<u>Number</u>	<u>IR^a</u>	<u>NMR^b</u>
<u>32</u>		7.40 (s,6), 4.20 (qt,4,J=7), 3.80 (s,3), 1.35 (t,6,J=7).
<u>33</u>	3010, 2940, 1730, 1260, 1035.	6.95 (dd,1,J=22.5, 9), 4.50- 3.96 (m,4) 3.80 (s,3), 3.00- 1.30 (m,11), 1.30 (t,6,J=7.5)
<u>34</u>	3000, 1730, 1260, 1030.	5.60 (m,1), 4.18 (qt,4,J=7.5), 3.82 and 3.87 (2s, total=3), 2.90- 1.80 (m,2), 1.32 (t,6, J=7.5), 1.60- 0.90 (m,5),
<u>35</u>		7.23 (dd,1,J=26, 2), 6.70 (dd,1,J=4, 2), 4.25 (qt,4,J=7), 3.88 (s,3), 1.37 (t,6,J=7).

a) Four most intense peaks.

b) See experimental for coding.

refluxed in toluene containing a small amount of toluene-sulfonic acid. Evaporation of the toluene and subsequent distillation afforded a 76% yield of 35. It should be noted that the synthesis of 35 has recently been accomplished by two other groups. Semmelhack (49) obtained 35 in 28% yield following the procedure of Pudovik (56), while Heathcock (48) prepared 35 in 82% overall yield using a selenium based method.

It was found that 31 would not condense with ketones under any conditions. When the reaction between 31 and both diethyl ketone and methyl isopropyl ketone, in refluxing toluene containing piperidine and glacial acetic acid was attempted, starting materials were recovered intact. Employing another approach, 31 was treated with sodium hydride, in ether solution at -78°C . Following the addition of acetone, the solution was quenched with methanol and allowed to come to room temperature. The ether was replaced with toluene, a small amount of toluenesulfonic acid was added and the solution heated at reflux for 8 hrs. Removal of the solvent gave a sticky brown solid. The nmr of this compound appeared to indicate that it was the desired phosphonate, however, when reacted with aldehyde 36, no dihydrothiophene was produced. No further studies involving the condensation of 31 with ketones were attempted.

Phosphonate 31 was prepared by an Arbuzov reaction between triethyl phosphite and methyl bromoacetate (Figure 19), employing the procedure of House (57). The methyl ester was

chosen to simplify the nmr spectra.

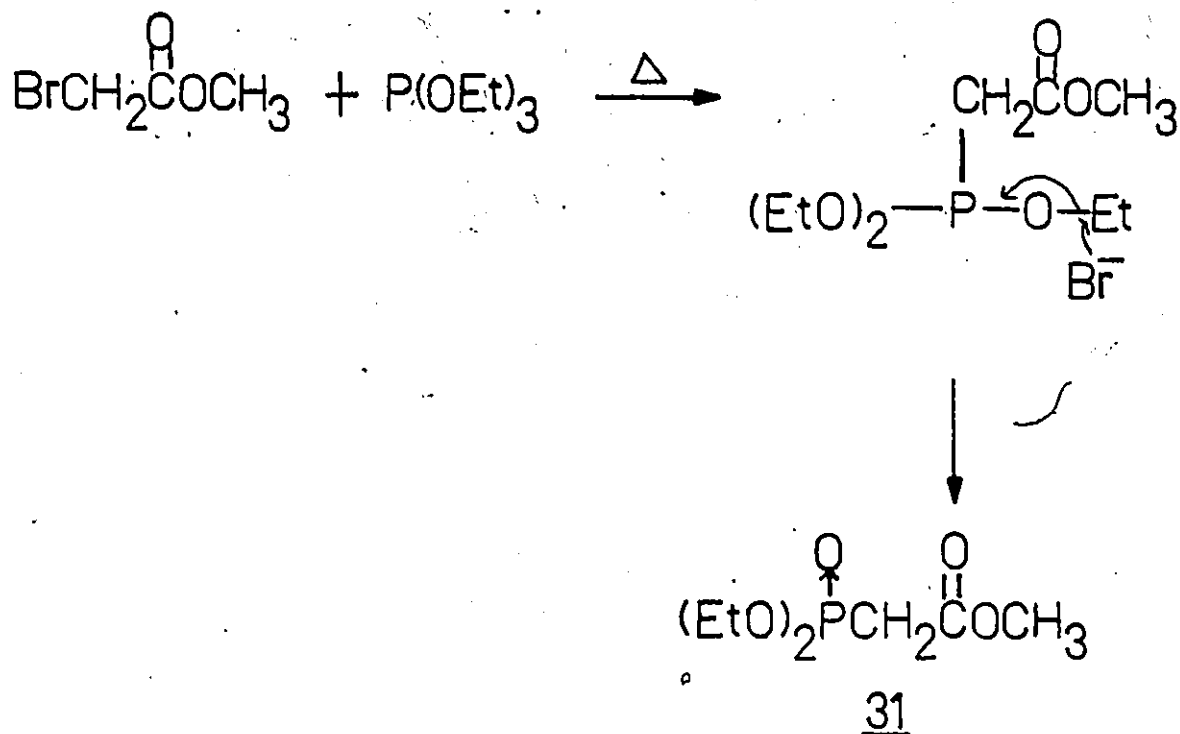


Figure 19. The Mechanism of The Formation of Methyl Diethylphosphonoacetate.

2,5- Dihydrothiophene Synthesis.

Initial studies were concentrated on the reactions of mercaptoaldehydes 36 and 38 with vinylphosphonates 32-35. The procedure which had proved successful with phosphonium salts was employed; i.e. refluxing a mixture of phosphonate, triethylamine and mercaptan in dry pyridine. The method proved viable for mercaptoaldehydes. However, when the reaction of mercaptoketone 37 and phosphonate 32 was attempted, no dihydrothiophene of any type was formed. The only product isolated, in very low yield, appeared to be the simple addition product 53. It was found to be advantageous to employ sodium hydride as the base in place



53

of triethylamine in reactions involving mercaptoketones. Removal of the solvent and diethyl phosphate from the products was accomplished by simple acid extraction. Coloured impurities were removed by passing the mixtures through a column of neutral alumina. Gas chromatographic analysis revealed product purity in excess of 95%. The results of the synthesis of eleven dihydrothiophenes are listed in Table 4, while the spectral data and physical properties of these compounds are summarized in Tables 5 and 6.

The reaction took an unexpected course in only one case. The condensation of 40 with 32 led to a low combined yield of two major products (Figure 20), which were glc-collected and identified as 54 and 55 on the basis of their spectral characteristics. A minor by-product appeared

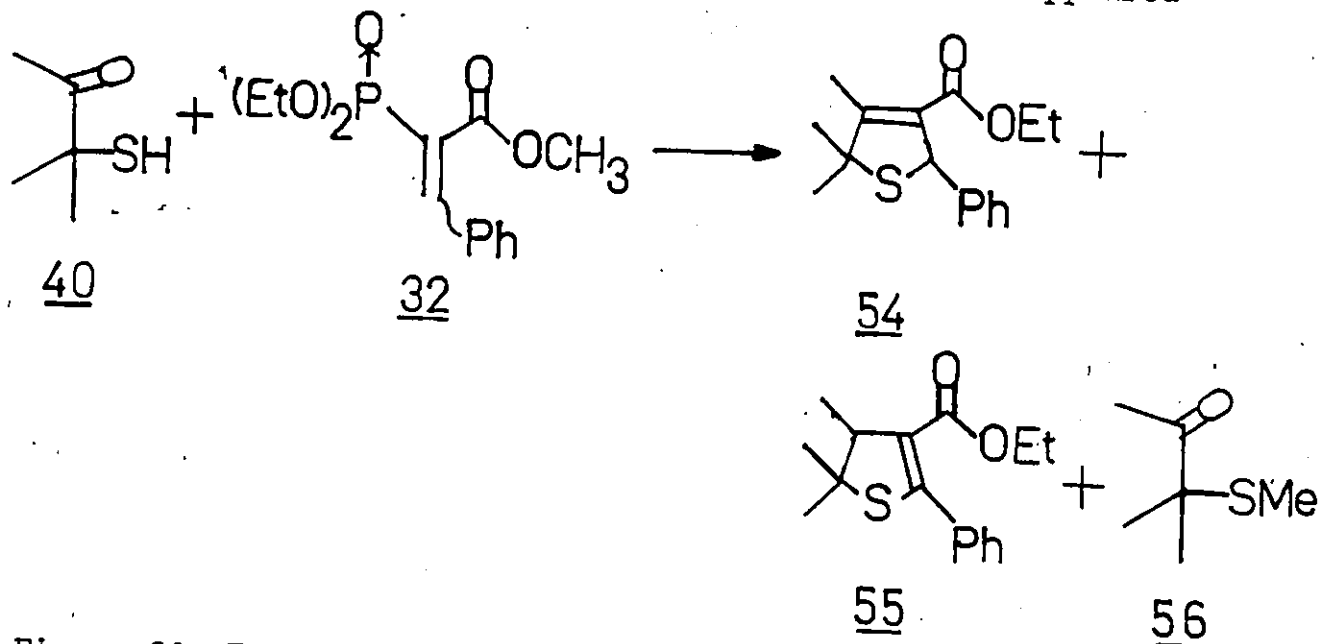


Figure 20. Formation of Isomers 54 and 55.

TABLE 3
Mercaptans

<u>Number</u>	<u>R₁</u>	<u>R₂</u>	<u>R₃</u>
<u>36</u>	Et	H	H
<u>37</u>	Me	H	Et
<u>38</u>	— (CH ₂) ₅ —		H
<u>39</u>	H	— (CH ₂) ₄ —	
<u>40</u>	Me	Me	Me
<u>41</u>	H	H	H

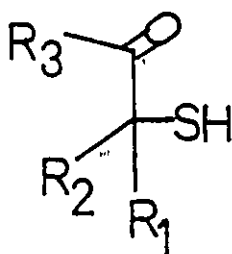


TABLE 4

Dihydrothiophenes Prepared

<u>Mercaptan</u>	<u>Phosphonate</u>	<u>Number</u>	<u>R₁</u>	<u>R₂</u>	<u>R₃</u>	<u>R₄</u>	<u>Yield(%)</u>
<u>36</u>	<u>35</u>	<u>42</u>	Et	H	H	H	71
<u>38</u>	<u>35</u>	<u>43^a</u>	$-(CH_2)_3$		H	H	94
<u>36</u>	<u>34</u>	<u>44</u>	Et	H	H	Pr	67
<u>38</u>	<u>34</u>	<u>45</u>	$-(CH_2)_3$		H	Pr	90
<u>40</u>	<u>34</u>	<u>46</u>	Me	Me	Me	Pr	81
<u>37</u>	<u>34</u>	<u>47</u>	Me	H	Et	Pr	54
<u>36</u>	<u>32</u>	<u>48</u>	Et	H	H	Ph	74
<u>38</u>	<u>32</u>	<u>49^b</u>	$-(CH_2)_3$		H	Ph	90
<u>39</u>	<u>32</u>	<u>50</u>	H	$-(CH_2)_4$		Ph	82
<u>36</u>	<u>33</u>	<u>51</u>	Et	H	H	C ₆ H ₁₁	86
<u>38</u>	<u>33</u>	<u>52</u>	$-(CH_2)_3$		H	C ₆ H ₁₁	89

a) mp 49-50°

b) mp 53-55° (recrystallized from hexane)

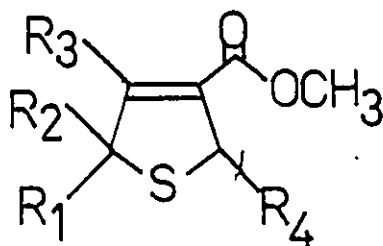


TABLE 5

Spectral Data For Dihydrothiophenes

<u>Number</u>	<u>N_D²⁵</u>	<u>IR^{a,b}</u>	<u>NMR^c</u>
<u>42</u>	1.5080	2970, 1715, 1440, 1265.	6.85 (dd, 1, J=3.7, 2), 4.35 (m, 1), 3.92 (dd, 2, J=3.7, 2), 3.80 (s, 3), 2.00-1.25 (m, 2), 1.01 (t, 3, J=7).
<u>43</u>	d	2940, 1720, 1440, 1250.	6.60 (t, 1, J=2), 3.85 (d, 2, J=2), 3.72 (s, 3), 1.95-1.00 (m, 10).
<u>44</u>	1.4942	2970, 1715, 1440, 1260.	6.72 (dd, 1, J=1.3, 3), 4.50-4.00 (m, 2), 3.75 (s, 3), 2.30-1.20 (m, 6), 1.20-0.80 (m, 6).
<u>45</u>	1.5141	2940, 1715, 1440, 1205.	6.75 (d, 1, J=1.5), 4.50-4.25 (m, 1), 3.80 (s, 3), 2.20-1.15 (m, 14), 1.00 (t, 3, J=6).
<u>46</u>	1.4936	2970, 1715, 1295, 1165.	4.40 (m, 1), 3.80 (s, 3), 2.06 (d, 3, J=1.5), 1.80-1.20 (m, 4), 1.55 (s, 3), 1.10-0.80 (m, 3).
<u>47</u>	1.4944	2970, 1715, 1440, 1290.	4.60-4.00 (m, 2), 3.80 (s, 3), 3.10-2.10 (m, 4), 1.80-0.75 (m, 11).

TABLE 5 (cont'd)

<u>Number</u>	<u>N_D²⁵</u>	<u>IR^{a, b}</u>	<u>NMR^c</u>
<u>48</u>	1.5436	3040, 1720, 1260, 1100.	7.20 (s, 5), 6.90 (dd, 1, J=5.8, 1.5), 5.46 (dd, 1, J=5.8, 1.5), 4.70-4.05 (m, 1), 3.57 (s, 3), 2.62-2.00 (m, 2), 1.05 (t, 3, J=6.5).
<u>49</u>	d	2930, 1720, 1285, 1265.	7.28 (s, 5), 6.85 (d, 1, J=2), 5.45 (d, 1, J=2), 3.52 (s, 3), 2.20-1.15 (m, 10).
<u>50</u>	1.5825	2950, 1715, 1285, 1265.	7.26 (s, 5), 5.56 (m, 1), 4.63-4.00 (m, 1), 3.56 (s, 3), 2.50-1.30 (m, 8).
<u>51</u>	1.5168	2940, 1715, 1265, 1100.	6.75 (bt, 1, J=1.5), 4.60-3.90 (m, 2), 3.75 (s, 3), 2.40-0.80 (m, 16).
<u>52</u>	1.5346	2930, 1715, 1450, 1255.	6.62 (d, 1, J=1.5), 4.48 (dd, 1, J=3, 1.5), 3.75 (s, 3), 2.40-0.80 (m, 21).

a) Four most intense peaks.

b) All compounds show medium strength absorption at 1650 cm^{-1} .

c) See experimental for coding.

d) Solid.

TABLE 6

Analytical Data

<u>Dihydrothiophene</u>	<u>Calculated</u>		<u>Found</u>	
	<u>C</u>	<u>H</u>	<u>C</u>	<u>H</u>
<u>42</u>	55.79	7.02	55.89	6.86
<u>43</u>	62.23	7.59	62.19	7.23
<u>44</u>	61.65	8.47	61.80	8.70
<u>45</u>	66.10	8.72	65.78	8.69
<u>46</u>	63.12	8.83	62.90	8.93
<u>47</u>	63.12	8.83	62.99	8.82
<u>48</u>	67.71	6.49	67.92	7.12
<u>49</u>	70.79	6.99	70.52	6.93
<u>50</u>	70.04	6.61	70.28	6.84
<u>51</u>	66.10	8.72	66.06	8.56
<u>52</u>	69.34	8.90	69.18	8.86

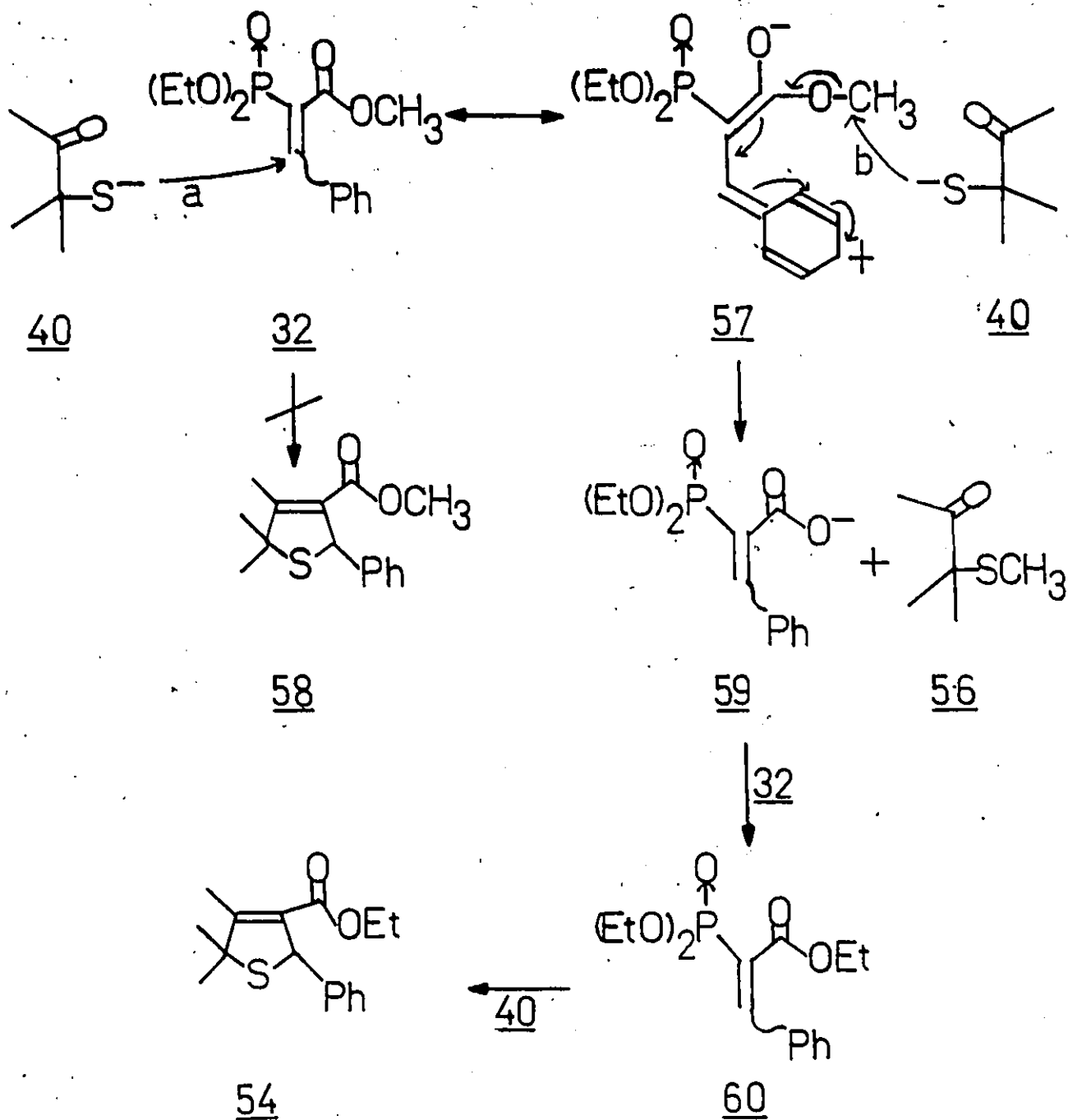


Figure 21. Proposed Mechanism of Formation of Isomer 54 .

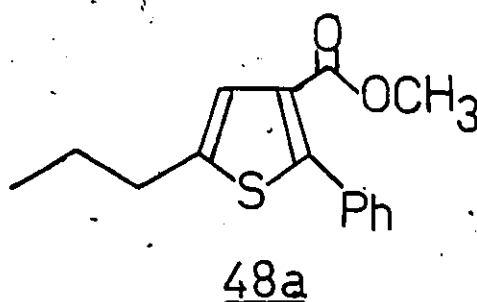
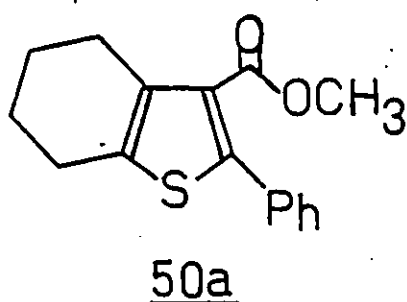
to be the S-methylated mercaptan 56. Identification of 56 was based on glc retention time, which was identical to that of the known compound prepared from 40 and methyl iodide.

While these results cannot be fully explained, a partial answer lies in the stability of the phosphonate involved. Assuming that the vinylphosphonate could exist as either 32 or 57, attack of the thiolate ion could occur at two possible sites (Figure 21). Where attack of the thiolate ion to occur via Path (a), the end result would have been the formation of dihydrothiophene 58. There was no evidence for the existence of 58. However, if attack of the thiolate ion occurred through Path (b), the end result would be the formation of the S-methylated mercaptan 56 and the anion of the phosphonate 59. Attack of 59 upon another molecule of 32 could produce ethyl 2-diethylphosphono-3-phenylacrylate (60). Michael addition of 40 to 60 followed by subsequent ring closure would produce dihydrothiophene 54. Thermal rearrangement of 54 (glc) could result in the isolation of 55.

It is interesting to note that ketone 39 reacted with 32 in the expected manner to produce dihydrothiophene 50 in excellent yield.

When ketones 40 and 37 were condensed with 34, dihydrothiophenes 46 and 47 were obtained as the only products in yields of 81% and 54% respectively. In two cases (50 and 48), the corresponding thiophenes

(50a and 48a) were formed as by- products. The structures were confirmed by comparison with authentic samples. Thiophene formation was eliminated by the rigorous exclusion of air from the reaction mixture.



Diene Synthesis

Having shown that the condensation of 2- mercapto- carbonyl compounds and vinylphosphonates leads to excellent yields of 3- carbomethoxy-2,5- dihydrothiophenes, it became necessary to test the proposed diene synthesis. While

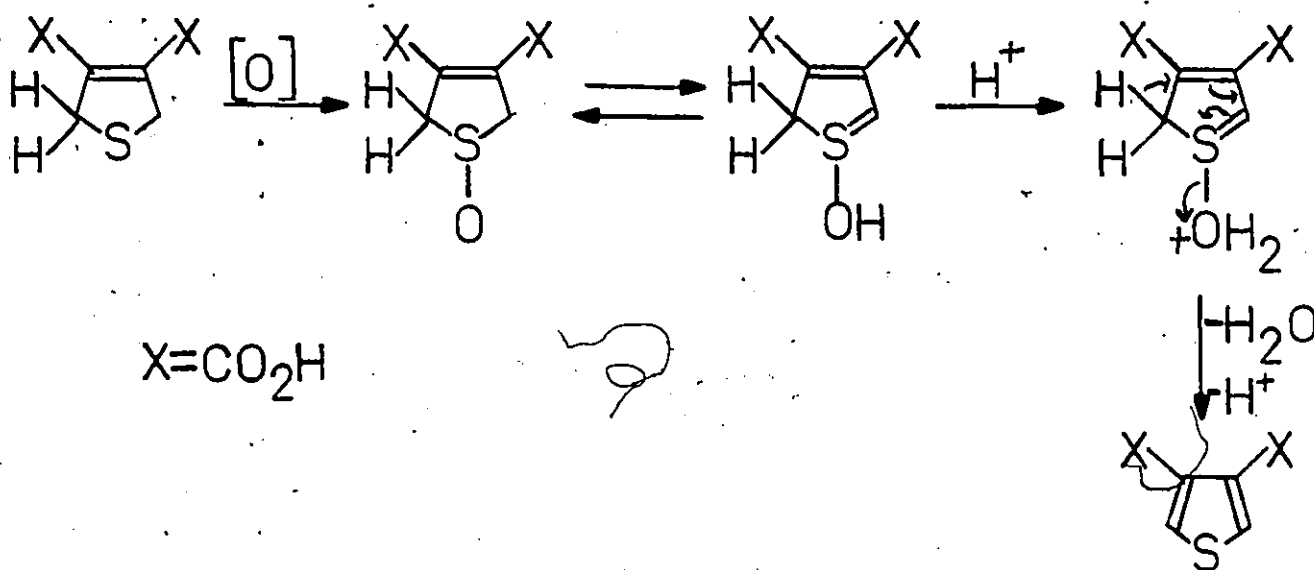
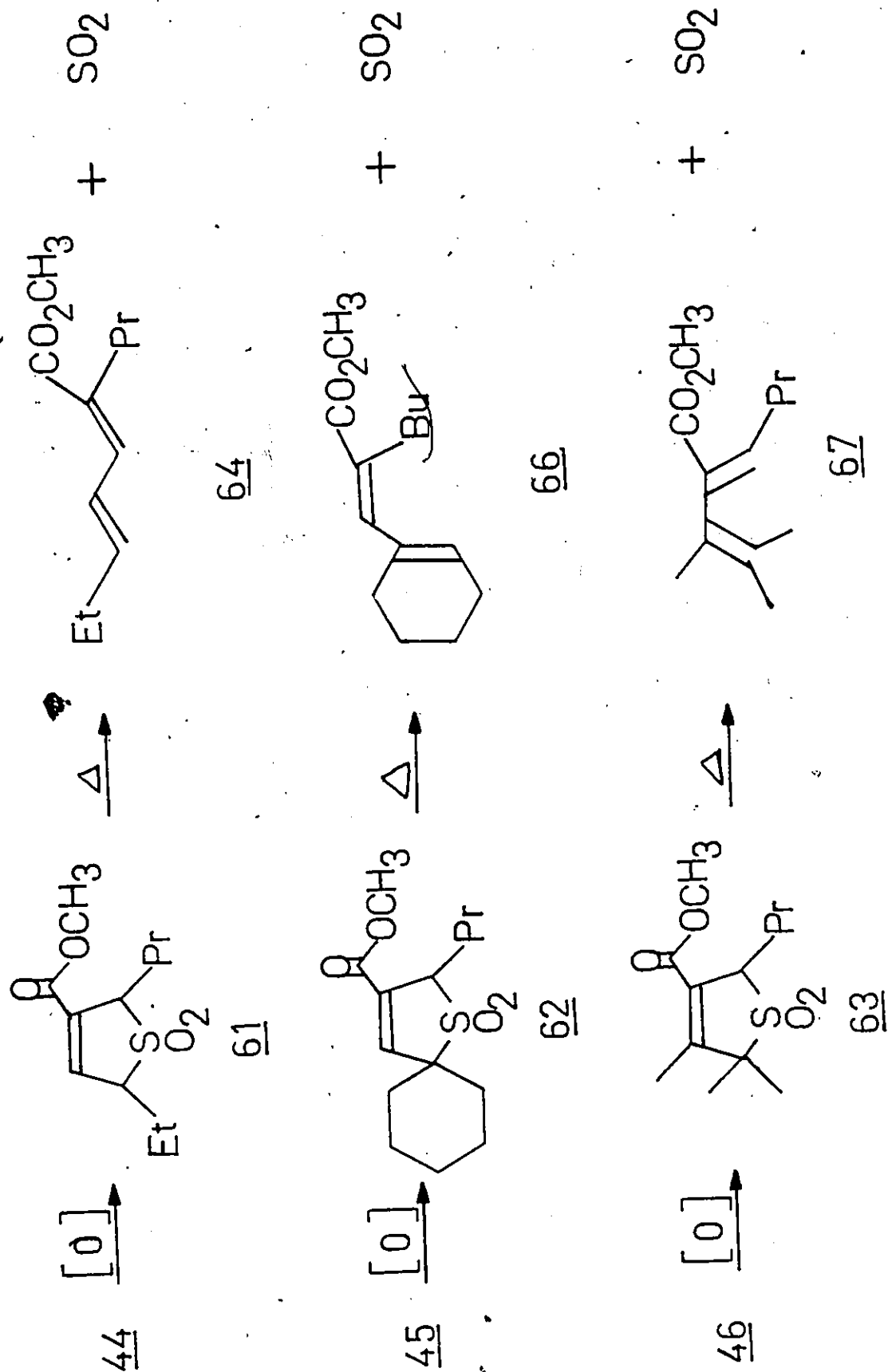


Figure 22. Peracid Oxidation of 2,5- Dihydrothiophenes
Resulting in Thiophene Formation.

Figure 23. Dienes Prepared.



the peracid oxidation of dihydrothiophenes normally leads to sulfones, there are cases known where thiophenes have been formed when the ring carries strongly electronegative substituents (23) (Figure 22).

Dihydrothiophenes 44- 46 were oxidized to sulfones 61- 63 using m- chloroperbenzoic acid. These were formed in near quantitative yields. Injection of the sulfones into the gas chromatograph effected elimination of sulfur dioxide and the dienes were collected directly (Figure 23).

Since the sulfones were obtained in nearly quantitative yield (96%) and sulfone pyrolysis proceeds in quantitative yield, it appears that the yields of dienes are excellent.

It has been noted in the literature that thermal [1,5] sigmatropic rearrangements have been observed in a number of substituted 1,3- dienes (58). This was an anticipated problem due to the column temperatures required to effect elimination of sulfur dioxide. Such a rearrangement was observed in the case of diene 65 (Figure 24). This isomerization may be

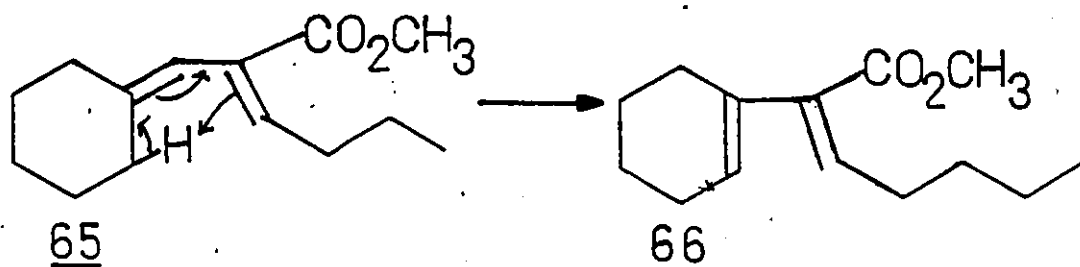


Figure 24. [1,5] Sigmatropic Rearrangement of Diene 65

avoided by conducting the pyrolysis at a lower temperature and in the presence of a dienophile. Spectral data and physical properties for dienes 64, 65 and 67 are found in Tables 7 and 8.

TABLE 7

Diene Products

<u>Dihydrothiophene</u>	<u>Sulfone</u>	<u>Diene</u> ^a	<u>IR</u> ^b	<u>NMR</u> ^c
<u>44</u>	<u>61</u>	<u>64</u>	2980, 1715, 1440, 1245.	6.60 (t, 1, J=7.5), 6.20-5.70 (m, 2), 3.80 and 3.75 (2s, total=3), 2.52- 1.97 (m, 4), 1.80- 1.25 (m, 2), 1.20- 0.75 (m, 6).
<u>45</u>	<u>62</u>	<u>66</u>	3050, 1720, 1245, 1210.	7.00 (s, 1), 5.85 (m, 1), 3.70 (s, 3), 2.60- 1.90 (m, 6), 1.81- 1.10 (m, 8), 0.87 (t, 3, J=6).
<u>46</u>	<u>63</u>	<u>67</u>	2970, 1710, 1270, 915.	5.85 (t, 1, J=7.5), 3.75 (s, 3), 2.48 (qt, 2, J=7.5), 1.74 (s, 6), 1.68 (s, 3), 1.60- 1.15 (m, 2), 0.90 (t, 3, J=6.7).

34

a) no stereochemistry implied.

b) four most intense peaks.

c) see experimental for coding.-

TABLE 8
Analytical Data For Dienes

<u>Diene</u>	<u>Calculated</u>		<u>Found</u>	
	<u>C</u>	<u>H</u>	<u>C</u>	<u>H</u>
<u>64</u>	72.49	9.95	72.19	10.21
<u>66</u>	75.63	9.97	75.54	9.98
<u>67</u>	73.43	10.27	73.21	10.13

Dihydrothiophenes Derived from α - Mercaptoacetaldehyde.

α - Mercaptoacetaldehyde (41), (59), (as the dimer) is an odiferous yellow solid with a melting point of 149-150°C. It has the added distinction of being insoluble in every common organic solvent other than pyridine.

When pyridine was employed as solvent and triethylamine as base, 41 consistently failed to give acceptable yields of product, a fact which was unfortunate as sulfone 13 was a precursor to 2- carbomethoxy-1,3- butadiene (14).

After extensive experimentation, still using pyridine as solvent, it was found that dihydrothiophene formation would occur at approximately 35°C. Discarding the use of pyridine as solvent in favor of methylene chloride was considered for two reasons.

1. The boiling point of methylene chloride is 40°C.
2. Methylene chloride had been employed as a solvent in the synthesis of 3,4- epoxy-2,5- dihydrothiophenes (60).

As stated earlier, 41 is completely insoluble in methylene chloride. Refluxing 41 in methylene chloride containing one equivalent of triethylamine had no apparent effect on the mercaptan. However, upon the addition of vinylphosphonate 33 an exothermic reaction occurred and the solution became homogeneous. After refluxing for six hours the solution was cooled. Simple acid extraction removed triethylamine and diethylphosphate. Dihydrothiophene 69 was obtained as the only product. In an identical manner were prepared dihydrothiophenes 12, 68 and 70 . The .

spectral data and physical properties of these are shown in Tables 9, 10 and 11.

The nature of the reaction of 41 with triethylamine was not investigated. From the results obtained, however, it appears that the reactive species 74 was formed (Figure 25).

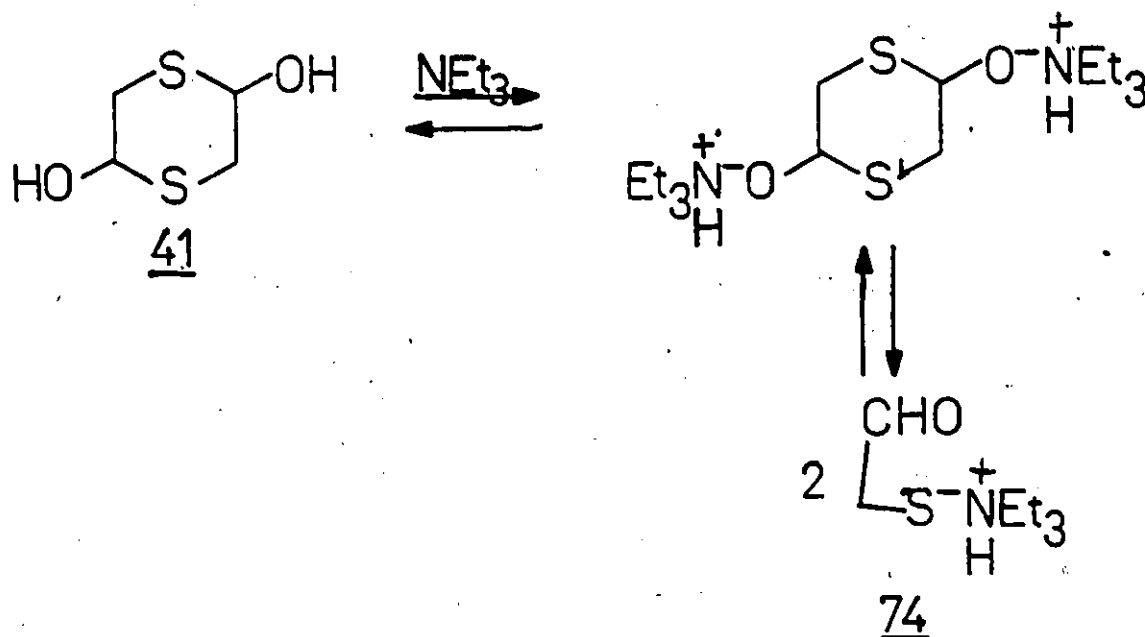


Figure 25. The Reaction of Mercaptan 41 with Triethylamine.

It is unknown at this time whether the solid observed before the addition of the phosphonate was undissolved 41 in equilibrium with 74, or 74 itself.

Employing refluxing methylene chloride and triethylamine, with mercaptoaldehydes 36 and 38 produced dihydrothiophenes in somewhat lower yield, but the products required substantially less purification. Mercaptoketones were not tested.

Peracid oxidation of dihydrothiophenes 12, 68-70 produced sulfones 13, 71-73, the yields, spectral data

TABLE 9

<u>Dihydrothiophenes Prepared From α-Mercaptoacetaldehyde</u>			
<u>Dihydrothiophene</u>	<u>R</u>	<u>MP(°C)</u>	<u>Yield(%)</u>
<u>12</u>	H	27- 28 ^a	68
<u>68</u>	Ph	66- 68	91
<u>69</u>	cyclohexyl	34- 35	88
<u>70</u>	n-propyl	b	83

a) bp 108-110/14 Torr.

b) non- crystalline.

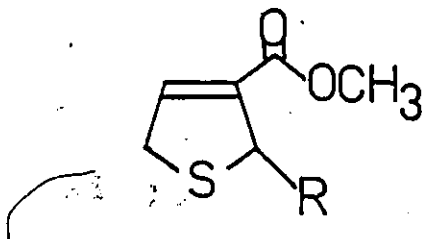


TABLE 10

Spectral Data of Dihydrothiophenes Prepared From α -Mercaptoacetaldehyde

<u>Dihydrothiophene</u>	<u>IR^a</u>	<u>NMR^b</u>
<u>12</u>	1725, 1445, 1275, 1090.	6.72 (bs, 1), 3.82 (s, 4), 3.68 (s, 3).
<u>68</u>	3020, 1725, 1650, 1275.	7.19 (s, 5), 6.97 (m, 1), 5.45 (m, 1), 4.00 (m, 2), 3.57 (s, 3).
<u>69</u>	2930, 1720, 1440, 1260.	6.95 (m, 1), 4.60-4.35 (bm, 1), 3.78 (s, 5), 2.30-0.90 (bm, 11).
<u>70</u>	2880, 1720, 1445, 1280.	6.85 (m, 1), 4.60-4.20 (m, 1), 3.77 (bs, 5), 2.08-1.13 (m, 4), 0.92 (t, 3, J=7).

a) Four most intense peaks.

b) See experimental for coding.

TABLE 11

Analytical Data

<u>Dihydrothiophene</u>	<u>Calculated</u>		<u>Found</u>	
	<u>C</u>	<u>H</u>	<u>C</u>	<u>H</u>
<u>12</u>	49.98	5.59	49.18	5.34
<u>68</u>	65.43	5.49	65.36	5.51
<u>69</u>	63.68	8.02	63.48	8.21
<u>70</u>	58.03	7.58	57.90	7.36

TABLE 12

Sulfones

<u>Dihydrothiophene</u>	<u>R</u>	<u>Product</u>	<u>M.P. (°C)</u>	<u>Yield (%)</u>
<u>12</u>	H	<u>13</u>	57-58 ^a	90
<u>68</u>	Ph	<u>71</u>	170-171(dec) ^b	84
<u>69</u>	cyclohexyl	<u>72</u>	96-98	87
<u>70</u>	n-propyl	<u>73</u>	42-43 ^a	86

a) Recrystallized from diethyl ether.

b) Recrystallized from DMSO- H₂O.

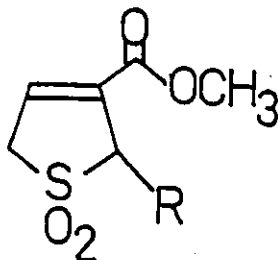


TABLE 13

Spectral Data For Sulfones

<u>Sulfone</u>	<u>IR^a</u>	<u>NMR^b</u>
<u>13</u>	3070, 1735, 1330, 1285	7.00 (m, 1), 3.98 (bs, 4), 3.80 (s, 3).
<u>71</u>	^c 1735, 1460, 1335, 1200.	^d 7.40 (m, 6), 5.46 (s, 1), 4.33 (d, 2, J=4), 3.90 (s, 3).
<u>72</u>	2940, 1735, 1330, 1280.	7.11 (t, 1, J=3), 3.82 (s, 6), 2.40-0.90 (bm, 11). ⁵
<u>73</u>	2990, 1735, 1330, 1280.	7.02 (t, 1, J=3), 4.02-3.70 (m, 3), 3.82 (s, 3), 2.20-1.20 (bm, 4), 0.93 (t, 3, J=7).

a) Four most intense peaks.

b) See experimental for coding.

c) KBr pellet.

d) in CF₃CO₂D solution.

and physical properties of which are shown in Tables 12 and 13. These sulfones, as their dihydrothiophene precursors, required little purification. Sulfones 13 and 73 were recrystallized from diethyl ether. Crude sulfone 71 was readily soluble in dimethyl sulfoxide, and deposited a tan colored powder upon the addition of water. This powder, after washing with diethyl ether and drying, was insoluble in dimethyl sulfoxide. Proton nmr of this material, in $\text{CF}_3\text{CO}_2\text{D}$ solution, indicated that it was the desired product. Sulfone 72 required no purification.

Diels- Alder Reactions of 2- Carbomethoxy-1,3- Butadiene

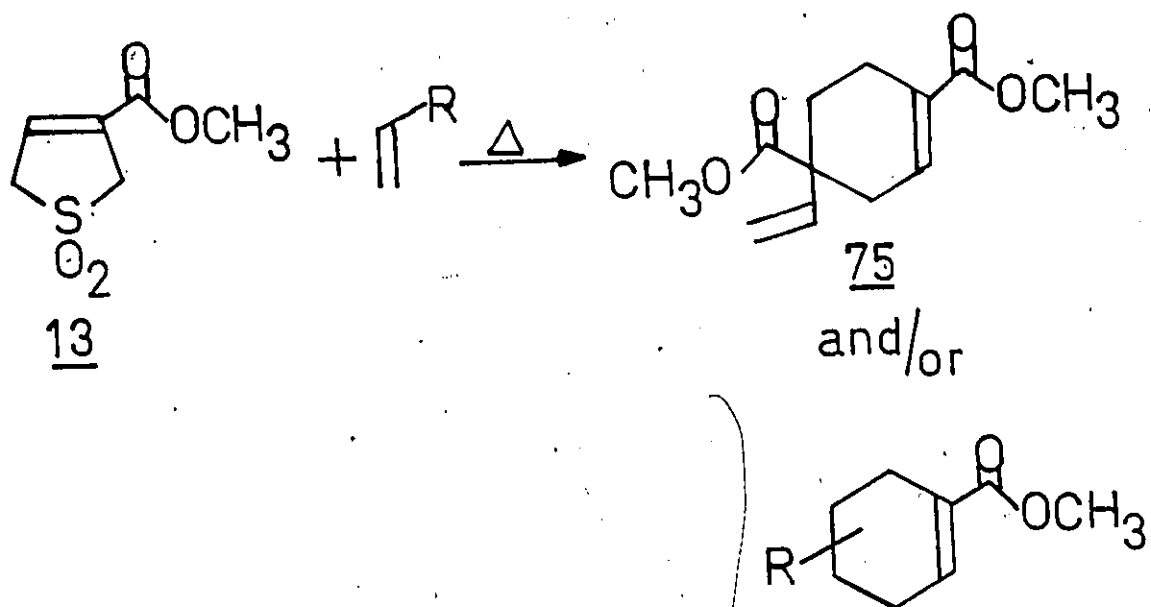


Figure 26. Regiochemistry of the Products Derived From the Diels- Alder Reactions of Diene 14 .

A stable precursor to diene 14 having been prepared, the final step in the project was to conduct a survey of the Diels- Alder reactions of 14 with various dienophiles

Sulfone 13 is a stable, white, crystalline compound

which melts at 57-58°C. When heated in toluene it decomposes moderately rapidly to form 14 and sulfur dioxide.

The initial reaction was one which involved 13 and cis-2-octene (Entry 7 Table 14). After evaporation of the solvent, unreacted cis-2-octene was recovered in quantitative yield. The residue, upon distillation, afforded the dimethyl ester (75) of mikanecic acid^a (61), (65). No trace of isomeric materials could be detected by gas chromatography or by proton or carbon nmr.

The absence of isomeric materials was not an unexpected result, for Dreiding (62) had recently prepared the diethyl ester of mikanecic acid and reported the formation of only one isomer. Related work on the dimerization of 2-cyano-1,3-butadiene (63), (64) has also been shown to result in only one regio-isomer. (Figure 27). When 13 was refluxed in toluene in the absence of added dienophile, 75 was obtained as the only product.

The reaction of 13 with maleic anhydride led to two products. When the product was allowed to crystallize from the reaction solvent (2 weeks at -6°C) the diacid was obtained. However, immediate removal of the solvent and washing the residue with ether afforded 76.

The condensation of 13 with ethyl acrylate (1 equivalent) led to a mixture of three products, 75 and 77 (65); 77 was formed as a mixture of two regio-isomers. Compounds 75 and 77 were inseparable by either glc or tlc. Using a ten-fold excess of ethyl acrylate eliminated the formation

a) IUPAC name: 1-cyclohexene-4-vinyl-1,4-dicarboxylic acid.

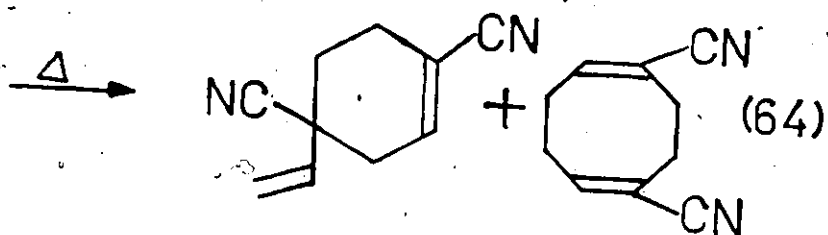
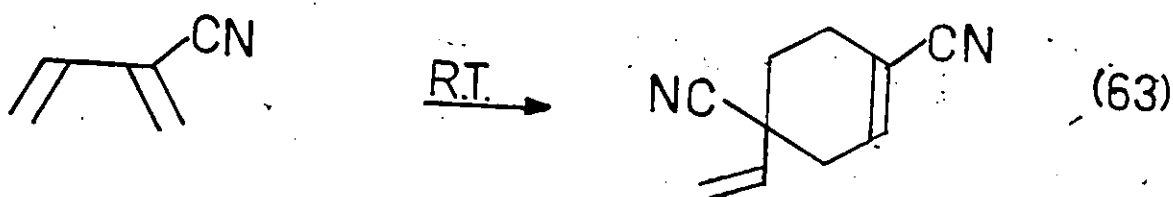
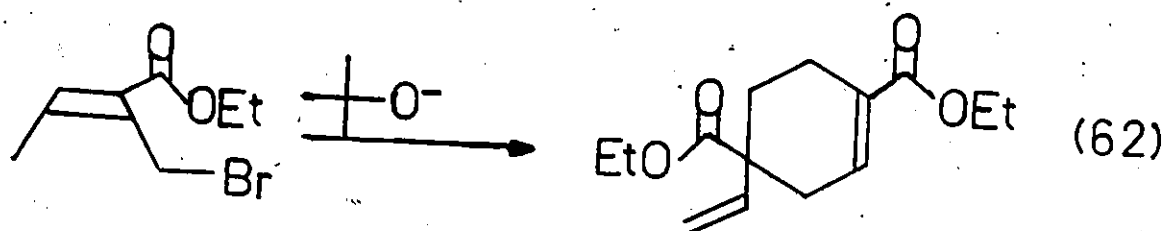
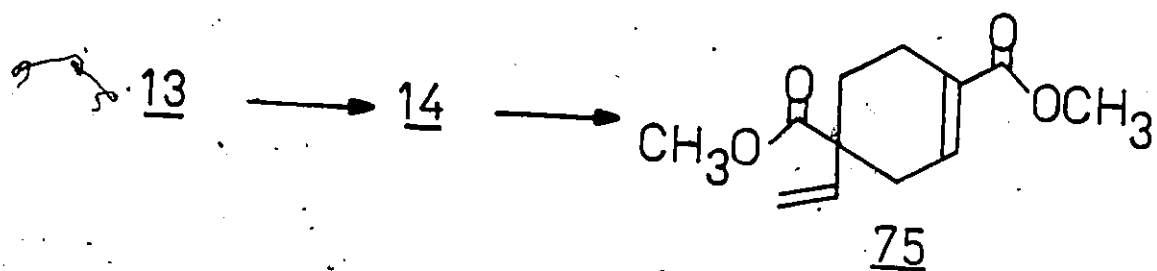
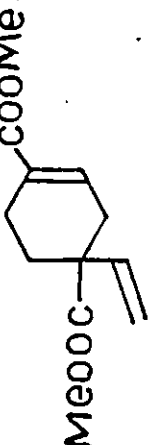

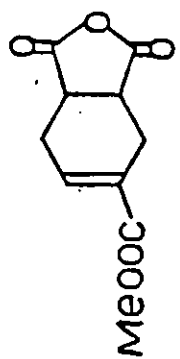
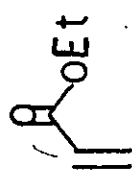
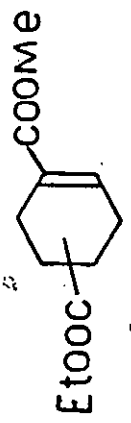
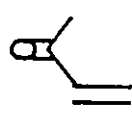
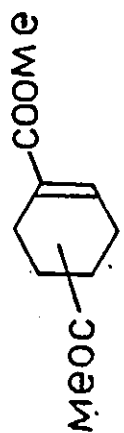


Figure 27. Self- Condensation of. 14 and 2- Cyano-1,3- Butadiene.

TABLE 14

Diels-Alder Reactions of 2-Carbomethoxy-1,3-Butadiene

<u>Run</u>	<u>Dienophile</u>	<u>Product</u>	<u>Yield(%)</u>	<u>Reference</u>
<u>1</u>	none		80 ^a	(61), (65)
<u>2</u>			73 ^b	
<u>3</u>			90 ^a	(65)
<u>4</u>			69 ^a	(66)

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TABLE 14 (cont'd)


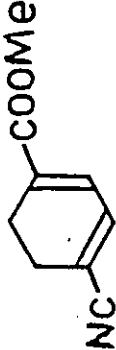
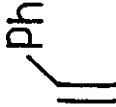
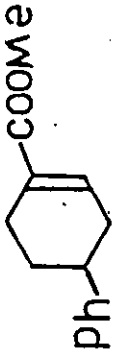
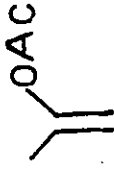


<u>Run</u>	<u>Dienophile</u>	<u>Product</u>	<u>Yield(%)</u>	<u>Reference</u>
<u>5</u>		 <u>79</u> + <u>75</u>	<u>43^a</u>	
<u>6</u>		 <u>80</u>	<u>26^a</u> <u>49^c</u>	(68)
<u>7</u>	2-octene	<u>75</u>	<u>70^d</u>	

TABLE 14 (cont'd)

<u>Run</u>	<u>Dienophile</u>	<u>Product</u>	<u>Yield(%)</u>	<u>Reference</u>
8		<u>75</u>	68 ^d	
9		<u>75</u>	98 ^a	
10		<u>75</u>	90 ^a	

a) chromatographed.

b) mp 110-111°C.

c) mp 34-37°C (recrystallized from hexane).

d) distilled bp 88-90°C/0.02 Torr. Lit(61) bp 120-121°C/1 Torr.

Lit(65) bp 110-113°C/0.80 Torr.

TABLE 15

Spectral Data of Diels- Alder Products

<u>Product</u>	<u>IR</u> ^a	<u>NMR</u> ^b
<u>75</u>	1730, 1715, 1440, 1275.	6.80 (m, 1), 6.00-4.80 (ABX mult., 3), 3.65 (s, 3), 3.60 (s, 3), 2.75-1.65 (m, 6).
<u>76</u>	1730-1715, 1440, 1335.	7.10 (m, 1), 3.73 (s, 3), 3.51 (m, 2), 3.00- 2.45 (m, 4).
<u>77</u>		6.85 (bs, 1), 4.10 (q, 2, J=7), 3.68 (s, 3), 2.60- 2.10 (m, 7), 1.26 (t, 3, J=7).
<u>78</u>		6.98 (m, 1), 3.70 (s, 3), 2.85-1.80 (m, 7), 2.18 (s, 3).
<u>79</u>	3000, 2200, 1725, 1430, 1280, 1230.	6.90 (AB quart., 1, J=5), 3.80 (s, 3), 2.58 (bs, 4).
<u>80</u>		7.27 (s, 5), 7.10 (m, 1), 3.73 (s, 3), 3.05- 1.65 (m, 7).

a) Most intense peaks.

b) See experimental for coding.

TABLE 16

Analytical Data For New Products

<u>Product</u>	<u>Calculated</u>		<u>Found</u>	
	<u>C</u>	<u>H</u>	<u>C</u>	<u>H</u>
<u>76</u> (as the diacid $C_{10}H_{12}O_6$)	52.63	5.30	52.96	5.34
<u>79</u>	66.25	5.56	65.60	5.44

TABLE 17

¹³C Absorptions of Diels- Alder Products

<u>Compound</u>	<u>Absorption</u>
<u>75</u>	174.94, 167.47, 139.86, 137.07, 129.86, 115.31, 52.36, 51.71. 47.62, 32.68, 29.88, 22.09, 19.88.
<u>76</u>	173.45, 173.12, 165.39, 137.78, 131.29, 52.09, 39.63, 38.78, 24.43.
<u>77</u>	176.18, 175.14, 167.54, 138.95 137.65, 130.25, 60.67, 57.71, 38.72, 28.19, 25.14, 23.78, 21.96, 14.42.
<u>78</u>	209.69, 167.21, 138.82, 137.71, 129.92, 51.45, 46.77, 46.19, 27.93, 27.15, 26.05, 25.34, 24.62, 23.91.
<u>80</u>	167.60, 145.97, 138.95, 130.31, 128.56, 126.81, 126.35, 51.38, 39.24, 33.78, 29.56, 24.95.

of 75. Compound 77 was still obtained as a mixture of regio- isomers as was shown by its ^{13}C spectra.

As indicated in Table 14 (Entry 5), the product isolated from the reaction of 13 and 2-chloroacrylonitrile was diene 79. The dehydrochlorination of the initial adduct is believed to have occurred during the reaction.

In general, it appears that diene 14 reacts well with electron- deficient dienophiles (runs 1-5) and styrene (run 6), but the desired condensation cannot compete with dimerization when using simple olefins (run 7) and more electron- rich materials (runs 8-10). These results are in contrast to the reported reactions of 2,3-dicyano-1,3-butadiene which reacts well with electron-rich and electron-deficient dienophiles (66). In the case of 14 there is apparently an insufficient electron deficiency to allow 14 to function in an "inverse electron demand"^a sense.

The regioselectivity of the Diels- Alder reactions of 14 appears to be variable. Although the presence of regioisomers was not confirmed by either proton nmr or glc analysis, carbon nmr of compounds 77 and 78 (67) clearly indicated the presence of more than two vinyl and three ring methylene carbon atoms. Since stereoisomerism is absent,

- a) Alder rules state that electron- rich dienes will preferentially react with electron- deficient dienophiles whereas "inverse electron demand" implies that electron-deficient dienes should react preferentially with electron- rich dienophiles.

these results can only be explained by the formation of regio- isomers. Similar investigation of 80 revealed no sign of extra absorption.

Summary and Conclusion

The synthesis of 3- carbomethoxy-2,5- dihydrothiophenes using α - mercaptoaldehydes and vinylphosphonates is conveniently accomplished when employing methylene chloride as solvent and triethylamine as base. α - Mercaptoketones necessitate the use of pyridine as solvent and sodium hydride as base.

The sulfones of 3- carbomethoxy-2,5- dihydrothiophenes are stable precursors to 2- carbomethoxy-1,3- conjugated dienes.

A survey of the Diels- Alder reactions of diene 14 indicates the inability to effect condensation with electron-rich dienophiles. The formation of regio- isomers limits the synthetic utility of 14, a problem which could possibly be alleviated by the use of Lewis acid catalysis (69).

CHAPTER 3

EXPERIMENTAL

GENERAL INFORMATION

Reagent grade chemicals were used without further purification unless otherwise specified. Pyridine was dried over sodium hydroxide pellets and was decanted prior to use. Methylene chloride was stored over molecular sieves. Melting points were taken on a Cenco apparatus and are uncorrected.

Nuclear magnetic resonance (nmr) spectra were recorded on a Jeolco C-60HL or Varian EM 360 spectrometer in deuteriochloroform solution. The chemical shifts are expressed in parts per million (δ) downfield from the internal standard tetramethylsilane (TMS). The splitting pattern of each resonance is reported according to the following code: s= singlet, d= doublet, t= triplet, q= quartet, qt= quintet, dd= doublet of doublets, m= multiplet and bs= broad singlet.

Infrared (ir) spectra were determined using a Beckman IR- 12 instrument, in chloroform solution and are reported in wavenumbers (cm^{-1}).

Electron impact mass spectra were recorded on a Varian MAT CH5- DF instrument.

Gas liquid chromatography (glc) analyses were carried

out on a Hewlett Packard 720 instrument equipped with a disc integrator. Helium carrier gas had a flow rate of 1 cc sec⁻¹. The following columns were used: A) 10' X .375" 20% SE- 30 on Chromosorb W; B) 8' X .375" 10% Dexsil on Chromosorb W.

Preparative thin layer chromatography was performed on 2 mm thick plates coated with silica gel GF- 270. Column chromatography utilized Fisher neutral alumina (80-200 mesh). The eluting solvent was 1:1 ether- pentane unless otherwise specified. Indices of refraction were measured using a Carl Zeiss refractometer. Anhydrous sodium sulfate was used as the drying agent in all cases. Solvents were removed on a rotary evaporator at reduced pressure, and under nitrogen. Elemental analyses were performed by A.B. Gygli, Microanalysis Laboratories Limited, Toronto, Ontario; Galbraith Laboratories, Inc., Knoxville, Tennessee and Spang Micro-analytical Laboratory, Eagle Harbor, Michigan. Analytical samples were glc- collected unless otherwise specified.

α - Mercaptocarbonyl Compounds 36- 40

These compounds had been previously prepared according to published procedures (25, 27).

α - Mercaptoacetaldehyde (41)

This mercaptan was purchased from the Aldrich Chemical Company.

Methyl Diethylphosphonoacetate (31)

This phosphonate was prepared according to a literature

procedure (57) using triethyl phosphite (107.9 g, 0.65 mol) and methyl bromoacetate (100.1 g, 0.65 mol). Distillation gave 110 g (80%) of product.

bp 95- 102/5 Torr. Lit(57) bp 113/9 Torr.

Methyl 2- Diethylphosphonoacrylate (35)

A variation of the literature was followed (56). Paraformaldehyde (6 g, 0.06 mol) and 0.50 g piperidine were added to 300 ml methanol and the solution heated to reflux. When the paraformaldehyde had dissolved, phosphonate 31 (20 g, 0.095 mol) was added, all at once, and refluxing continued for 19 hrs. The methanol was evaporated to afford an oil, the nmr of which showed no vinyl absorption. The oil was dissolved in 200 ml toluene, a catalytic amount of toluenesulfonic acid was added, and the solution refluxed under a Dean-Stark trap for 8 hrs. The solvent was removed and the residue distilled to give 16 g (76%) of 35.

bp 92- 94/0.08 Torr. Lit(49) bp 95- 98/0.15 Torr.

Lit(56) bp 100- 101/1 Torr.

Methyl 2- Diethylphosphono-2-hexenoate (34)

This phosphonate was prepared by a variation of the literature procedure (55). To a 300 ml round- bottom flask containing 150 ml benzene was added phosphonate 31 (22 g, 0.104 mol), 0.50 g piperidine, 2 ml acetic acid and butyraldehyde (6.5 g, 0.09 mol). A Dean- Stark trap and reflux condenser were attached. The Dean- Stark trap was filled with a 50% v/v mixture of butyraldehyde and benzene.

The solution was stirred at room temperature for 2 hrs, then refluxed for 24 hrs. The solvent and excess butyraldehyde were evaporated and the remaining oil distilled to provide 24 g (87%) of product.
bp 96- 102/0.05 Torr.

Methyl 2- Diethylphosphonocinnamate (32)

A literature procedure (55) was followed. To a stirred solution of benzaldehyde (25 g, 0.236 mol) and phosphonate 31 (30 g, 0.143 mol) in 150 ml benzene was added a mixture of 3.5 ml acetic acid and 0.50 g piperidine. The solution was heated at reflux under a Dean- Stark trap for 22 hrs. The solvent was removed and the residue distilled to give 30 g (70%) of product.
bp 160- 165/1 Torr.

Methyl 2- Diethylphosphono-3-cyclohexylacrylate (33)

This phosphonate was prepared in the manner of 32. From 31 (30 g, 0.143 mol) and cyclohexanecarboxaldehyde (18 g, 0.161 mol) was obtained 42 g (97%) of 33.
bp 120- 122/0.02 Torr.

Spectral data for the phosphonates are given in Table 2.

Preparation of Dihydrothiophenes

Method A: For Mercaptoaldehydes

To a solution of .01 mol phosphonate and .013 mol triethylamine in 75 ml dry pyridine was added a solution of .01 mol of the appropriate aldehyde in 25 ml pyridine, dropwise with stirring and under nitrogen. The mixture was

stirred at room temperature for 1 hr, refluxed 16 hrs, cooled and diluted with 200 ml water. The solution was extracted with ether (4 X 50 ml) and pentane (4 X 50 ml). The combined organic extracts were washed with 10% hydrochloric acid solution, water and then dried. The solvent was evaporated to afford a dark brown oil which was purified by column and then thin- layer chromatography.

Method B: For Mercaptoketones

To a stirred slurry of oil- free sodium hydride (0.012 mol) in 50 ml dry pyridine and under nitrogen was added, dropwise, a solution of 0.01 mol of the appropriate ketone, in 25 ml pyridine. After hydrogen evolution had ceased, the appropriate phosphonate, in 25 ml pyridine, was added dropwise and stirring was continued for 1 hr. After refluxing for 18- 20 hrs, the solution was cooled and worked up as above.

The eleven dihydrothiophenes prepared by either Method A or Method B are listed in Table 4. Spectral Data and physical properties are given in Tables 5 and 6.

Formation of Isomers 54 and 55

When the reaction between 40 and 32 was carried out using the sodium hydride procedure, an oil was obtained which contained two major components. These were separated by glc and shown to be 3- carboethoxy-2- phenyl-4,5,5-trimethyl-2,5- dihydrothiophene (54); nmr: 7.32 (s,5), 5.55 (q,1,J=1.8), 4.05 (d,q,2,J=7, 2), 2.20 (d,3,J=1.8),

1.62 (s,3), 1.58 (s,3), 0.97 (t,3,J=7) and 3- carboethoxy-2- phenyl-4,5,5- trimethyl-4,5- dihydrothiophene (55); mp 49- 51°C; nmr: 7.27 (s,5), 3.98 (q,2,J=7), 3.09 (q,1,J=6.7), 1.57 (s,3), 1.40 (s,3), 1.25 (d,3,J=6.7), 1.00 (t,3,J=7); m/e 276 (M^+ , 100%); ir: 2990, 1690,1330,4265.

Method C: For α - Mercaptoacetaldehyde

In a typical experiment, to α - mercaptoacetaldehyde (0.01 mol), stirring in 50 ml methylene chloride and under nitrogen was added triethylamine (0.013 mol). The solution was heated to reflux and the appropriate phosphonate (0.01 mol) was added dropwise, and refluxing continued for 4 hrs. The solution was cooled, diluted with a further 100 ml methylene chloride and washed with 5% hydrochloric acid (2 X 100 ml), dried, and the solvent evaporated. The residue was chromatographed on alumina using methylene chloride as the eluting solvent. In the case of dihydrothiophene -12, the product was distilled. bp 108- 110°C/14 Torr. mp 27-28°C.

The reaction may be easily scaled up to twenty times this size. Yields of the four dihydrothiophenes prepared from α - mercaptoacetaldehyde are given in Table 9. Spectral data and physical properties are summarized in Tables 10 and 11.

Peracid Oxidation of Dihydrothiophenes

The oxidation was carried out according to a published procedure (27). In a representative experiment, a stirred solution of 12 (18.08 g, 0.126 mol) in 800 ml methylene chloride and under nitrogen was cooled to -10°C in an ice-

salt bath. To this solution was added m- chloroperbenzoic acid (43.3 g, 0.253 mol), in small portions. The solution was stirred at -10°C for 1 hr and at ambient temperature for 24 hrs. After filtration, the organic layer was washed with saturated sodium carbonate solution (4 X 200 ml), dried and the solvent evaporated. The residue was triturated with cold diethyl ether to give 20.50 g (92%) of sulfone 13 . mp $57-58^{\circ}\text{C}$.

Sulfones 71-73 and 61-63 were prepared in an analogous manner, but on a 0.01 mol scale. Yields and physical properties of sulfones 13, 71-73 are recorded in Table 12. Spectral data is given in Table 13. Sulfones 61-63 were not characterized, but injected directly into the glc.

Sulfone Pyrolysis

Injection of crude sulfones 61-63 into the glc (column A) effected elimination of sulfur dioxide and the dienes were collected directly. Spectral data and physical properties for the products are given in Tables 7 and 8.

General Procedure For The Diels- Alder Reactions of 13

Sulfone 13 (1.76 g, 0.01 mol) was dissolved in 30 ml toluene. To this stirred solution was added 0.10 mol of the appropriate dienophile (in the case of maleic anhydride only 0.01 mol was used) and a small amount of hydroquinone. The solution was refluxed overnight. The solvent and excess dienophile were removed at reduced pressure and the residue was chromatographed on alumina using ether as eluent. Products

and yields are given in Table 14. Spectral data and physical properties are recorded in Tables 15 and 16. ^{13}C spectral data for the products is given in Table 17.

REFERENCES

1. M.C. Kloetzel, Org. Reactions, 4, 10 (1962).
2. O. Diels and K. Alder, Ann., 460, 98 (1928).
3. For a complete list, see H.O. House, "Modern Synthetic Reactions", 2nd ed., W.A. Benjamin, New York, NY., (1972), p817.
4. R.B. Woodward, Tetrahedron, 2, 1 (1958).
5. L.H. Sarett, J. Am. Chem. Soc., 74, 4974 (1952).
6. E.E. van Tamelen, J. Am. Chem. Soc., 80, 5006 (1958).
7. O. Grummitt and E.I. Becker, Org. Syntheses, Coll. Vol. 4, 771 (1963).
8. W. Herz and E. Lewis, J. Org. Chem., 23, 1646 (1958).
9. G.A. Grob, Helv. Chim. Acta, 40, 130 (1957).
10. For a general review of the Wittig reaction see A. Maercker, Org. Reactions, 14, 270 (1965).
11. R.J. Sundberg, P.A. Bukorvick and F.O. Holcombe, J. Org. Chem., 32, 2938 (1967).
12. B.M. Trost, J. Am. Chem. Soc., 96, 7165 (1974).
13. J. Tsuji, T. Yamakawa, M. Kaito and T. Mandai, Tetrahedron Lett., 2075 (1978).
14. L.W. Newton and E.R. Coburn, Org. Syntheses, Coll. Vol. 3, 312 (1955).
15. J. Mulzer, U. Kuhl and G. Bruntrop, Tetrahedron Lett., 2953 (1978).
16. W.L. Mock, J. Am. Chem. Soc., 88, 2857 (1966).

17. S.D. McGregor and D.M. Lemal, J. Am. Chem. Soc., 88, 2858 (1966).
18. P. Chao and D.M. Lemal, J. Am. Chem. Soc., 95, 920 (1973).
19. R.C. Krug and D.E. Boswell, J. Heterocyclic Chem., 4, 309 (1967).
20. P.L. Stotter, S.A. Roman and C.L. Edwards, Tet. Lett., 4071 (1972).
21. S.F. Birch and D.T. McAllan, J. Chem. Soc., 2256 (1951).
22. R.C. Krug and S. Tocker, J. Org. Chem., 20, 1 (1955).
23. T. Takaya, Bull. Chem. Soc. Japan, 41, 2086 (1968).
24. J.M. McIntosh, H.B. Goodbrand and G.M. Masse, J. Org. Chem., 39, 202 (1974).
25. J.M. McIntosh and R.S. Steevensz, Can. J. Chem., 52, 1934 (1974).
26. J.M. McIntosh and R.S. Steevensz, Can. J. Chem., 55, 2442 (1977).
27. J.M. McIntosh and G.M. Masse, J. Org. Chem., 40, 1294 (1975).
28. J.M. McIntosh and H. Khalil, Can. J. Chem., 53, 209 (1975).
29. H. Katsuki, J. Org. Chem., 43, 1471 (1978).
30. D.N. Reinholdt, Tetrahedron Lett., 4777 (1976).
31. R. Helder and H. Wynberg, Tetrahedron Lett., 605 (1972).
32. H.J. Kuhn and K. Kollnick, Tetrahedron Lett., 1909 (1972).
33. G.R. Pettit and E.E. van Tamelen, Org. Reactions, 12, 356 (1962).
34. J.F. Biellman and J.B. Ducep, Tetrahedron, 27, 5861 (1971).
35. J.M. McIntosh and C.K. Schram, Can. J. Chem., 55, 3755 (1977).

36. G. Jones, Org. Reactions, 15, 204 (1967).
37. T. Tsuanetsugu, T. Fueno and J. Furukawa, Makromol. Chem., 112, 220 (1968).
38. G. Stork and P.L. Stotter, J. Am. Chem. Soc., 91, 7780 (1969).
39. J.M. McIntosh and H.B. Goodbrand, Synthesis, 862 (1974).
40. For a detailed list, see Ref. 10, p451.
41. G. Wittig and H. Reiff, Angew. Chem. Int. Ed. Engl., 7, 7 (1968).
42. S. Trippet and D.M. Walker, Chem. and Ind., 990 (1965).
43. See Ref. 10, p270.
44. V. Subramanyan, E.H. Silver and A.H. Solway, J. Org. Chem., 41, 1272 (1976).
45. W.S. Wadsworth and W.D. Emmons, J. Am. Chem. Soc., 83, 1733 (1961).
46. F. Ramirez and S. Dershowitz, J. Org. Chem., 22, 41 (1957).
47. S.D. Darling and N. Subramanian, J. Org. Chem., 40, 2851 (1975).
48. W.A. Kleschick and C.H. Heathcock, J. Org. Chem., 43, 1256 (1978).
49. M.F. Semmelhack, J.C. Tomesch, M. Czárny and S. Boettger, J. Org. Chem., 43, 1259 (1978).
50. W.S. Wadsworth, Org. Reactions, 25, 77 (1977).
51. G.M. Kosolopoff, "Organic- Phosphorus Compounds", 1st Ed., Wiley and Sons Inc., New York, N.Y., 1950, p121.
52. For a more complete list, see D.C. Wysocki, PhD. Thesis, University of Pittsburgh, Pittsburgh, PA. (1967); Diss. Abstr. B, 28, 1437 (1967); Ref 50 p139.

53. H. Khalil, Ph.D. Thesis, University of Windsor, Windsor, Ontario, Canada, 1977.
54. A.N. Pudovik and N.M. Lebedeva, Dokl. Akad. Nauk S.S.S.R., 90, 709 (1953).
55. S. Patai and A. Schwartz, J. Org. Chem., 25, 1232 (1960).
56. A.N. Pudovik, V.I. Nikitina and A.M. Kurguzova, J. Gen. Chem. U.S.S.R., (Engl. Transl.), 40, 261 (1970).
57. H.O. House, V.K. Jones and G.A. Frank, J. Org. Chem., 29, 3327 (1964).
58. D.S. Glass, R.S. Boikess and S. Winstein, Tetrahedron Lett., 999 (1966).
59. commercially available from the Aldrich Chemical Company.
60. J.M. McIntosh and H. Khalil, J. Org. Chem., 42, 2123 (1977).
61. L.A. Yanovskaya, Zh. Obshchei Khim., 30, 3972 (1960).
62. O. Goldberg and A.S. Dreiding, Helv. Chim. Acta, 59, 1904 (1976).
63. C.S. Marvel and N.O. Brace, J. Am. Chem. Soc., 71, 37 (1949).
64. F.J. Weigert, J. Org. Chem., 42, 3859 (1977).
65. H. Sperber, Justus Liebigs Ann. Chem., 583, 161 (1953).
66. R.L. Cobb, V.C. Vives and J.E. Mahan, J. Org. Chem., 43, 931 (1978).
67. A.A. Dravkina, O.V. Epimova and Yu.S. Tsizin, J. Gen. Chem., U.S.S.R., 42, 1129 (1972).
68. K. Morita, Japanese patent #68-29, 136; Chem. Abs. 70, 77441 (1969).
69. for example G.I. Fray and R. Robinson, J. Am. Chem. Soc., 83, 249 (1961); C.F.H. Allen, J. Org. Chem., 27, 778

(1962); T. Inukai and M. Kasai, J. Org. Chem., 30, 3567
(1965):

VITA AUCTORIS

Name: Robert Alan Sieler

Birthdate: February 18, 1953; Leamington, Ontario.

Education:

Gosfield North Central School, Cottam, Ont. 1959-1967

Essex District High School, Essex, Ont. 1967-1972

University of Windsor, Windsor, Ont. 1972-1976

Degree: B.Sc. (Honours Chemistry)

University of Windsor, Windsor, Ont. 1976-1979

Degree: M.Sc. (Organic Chemistry)

Publications:

Synthesis of 3- Carboxylated-2,5- Dihydrothiophenes,
J.M. McIntosh and R.A. Sieler, Can. J. Chem., 56,
226 (1978).

Professional Affiliations:

Chemical Institute of Canada.